STATE OF SOUTH DAKOTA	)	IN CIRCUIT COURT
	:SS	
COUNTY OF MINNEHAHA	)	SECOND JUDICIAL CIRCUIT

CHARLES RUSSELL RHINES, Plaintiff, v. SOUTH DAKOTA DEPARTMENT OF CORRECTIONS, MIKE LEIDHOLT, SECRETARY, SOUTH DAKOTA DEPARTMENT OF CORRECTIONS, AND DARIN YOUNG IN HIS CAPACITY AS WARDEN OF THE SOUTH DAKOTA STATE PENITENTIARY, Defendants.	49CIV. 19-002940 **THIS IS A CAPITAL CASE EXECUTION SET FOR BETWEEN NOVEMBER 3, 2019 AND NOVEMBER 9, 2019**

REPLY/SUPPLEMENTAL MEMORANDUM OF LAW IN FURTHER SUPPORT OF APPLICATION FOR A PRELIMINARY INJUNCTION, TEMPORARY RESTRAINING ORDER AND STAY OF EXECUTION

As this Court identified at the onset of yesterday's hearing, the ultimate issue in this case is whether pentobarbital is an ultra-short-acting barbiturate. Plaintiff Charles Russell Rhines ("Rhines") has demonstrated overwhelmingly that it is not, and no court or medical authority has classified pentobarbital as such. The immediate issue here, however, is whether Plaintiff Rhines has demonstrated a likelihood that pentobarbital is not an ultra-short-acting barbiturate such that a stay of the irreparable is warranted considering the other equitable factors. Given such overwhelming demonstration, the Court should answer the immediate issue in the affirmative and grant Rhines' Application for a Preliminary Injunction, Temporary Restraining Order and Stay of Execution.

This brief and supplemental affidavit are submitted pursuant to the Court's invitation to file any additional arguments or information. These supplemental fillings will briefly respond to

some of the arguments raised in Defendants' response to Mr. Rhines's application, as well as provide additional information that it critical to this application.

I. Pentobarbital Is Not an Ultra-Short Acting Barbiturate

As an initial matter, in reviewing the medical documents and testimony regarding barbiturates, the Court should ignore such documents and testimony that relate to the *effects* of the drugs because that is not the issue here. When drafting SDCL § 23A-27A-32 (1984), the legislature set forth a specific *classification* of a barbiturate to be used - those classified as ultra-short-acting. The statute did not concern itself the effects of drugs nor did it defer to the South Dakota Department of Corrections to choose the drugs and the doses to accomplish the desired effects. With no authority classifying pentobarbital as an ultra-short-acting barbiturate and without an expert witness to testify to the same, Defendants attempt to create an alternative classification system based on the effects of the drugs given certain doses and in certain settings rather than the universal classification based on the drugs' chemical properties. To that end, Defendants carefully extract testimony and literature in the context of the effects of barbiturates and not the classification. When looking at the evidence on the classification, which is the exercise here, it is overwhelmingly true that pentobarbital is not an ultra-short-acting barbiturate.

As Dr. Craig Stevens testified and explained, barbiturates are classified as either ultra-short-acting, short-acting, intermediate-acting, or long-acting, depending upon their chemical properties, to wit, how lipid-soluble a particular barbiturate is. He is not aware of any peer reviewed articles or medical literature that has ever classified pentobarbital as an ultra-short-acting barbiturate. He testified that in his expert opinion, pentobarbital is not an ultra-short-acting barbiturate. His opinion is consistent with authoritative medical texts and articles. *See, e.g.*, Linda Lilley, et al., Pharmacology and the Nursing Process 189 (9th ed. 2020) (including classification

chart listing thiopental as ultrashort-acting barbiturate and pentobarbital as short-acting barbiturate); PHARMACOLOGY 111 fig. 9.7 (Richard A. Harvey & Pamela C. Champe eds.) (4th ed. 2009) (classifying pentobarbital as short-acting and thiopental as ultra-short-acting); Carl Burtis et al., Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 1325-26 & Table 34.10 (4th ed. 2006) (identifying thiopental as ultrashort-acting barbiturate and pentobarbital as short-acting barbiturate); Francisco López-Muñoz, et al., The History of Barbiturates a Century After Their Clinical Introduction, NEUROPSYCHIATRIC DISEASE AND TREATMENT, Vol. 1(4), 329-43, Table 3 (Dec. 2005) (reproducing table from 1983 classifying pentobarbital as short-acting and thiopental as ultrashort-acting); *see also* 1 Lawyers' Guide to Medical Proof § 106.02 (2019) (classifying ultrashort-acting barbiturates "in current medical use" as methohexital, thiamylal, and thiopental, and classifying pentobarbital among the short-acting and intermediate-acting barbiturates); 9 Attorneys Textbook of Medicine (Third Edition) P. 51.10 (2019) (classifying ultrashort-acting barbiturates as thiopental, thiamylal and methohexital); 12-256-9A Courtroom Medicine Series: Psychic Injuries § 9A.50 ("Ultra-short-acting barbiturates include thiopental (half-life of 6 to 46 hours; Schedule III) and methohexital (1 to 2 hours; Schedule IV); the short-acting group includes pentobarbital (Nembutol; 15 to 48 hours; Schedule II; III) . . . .").

The affidavit of Dr. Antiognini, submitted by the Defendants, does not contradict this.[1] Rather than arguing against the universally-accepted classification of pentobarbital, Dr. Antiognini focuses on the "desired clinical effect (e.g. unconsciousness)" of pentobarbital compared to other drugs at different doses. See Ex. D to Antiognini affidavit. In other words, Dr. Antiognini cannot

[1] If Defendants submit a supplemental affidavit from Dr. Antognini that states that pentobarbital has been classified as an ultra-short-acting barbiturate, this Court should grant the motion for an injunction to allow counsel for Mr. Rhines to depose Dr. Antiognini. The crux of the complaint and motion are whether pentobarbital is classified as an ultra-short-acting barbiturate, and if Dr. Antiognini did not testify to that in his first affidavit, counsel for Mr. Rhines is entitled to test any newly formed opinion.

argue against the chemical properties of pentobarbital, namely its lipid-solubility, that prevent it from being classified as ultra-short-acting and, instead, argues a position not contemplated by SDCL § 23A-27A-32 (1984) – that, if the warden gets the dose right, it will have the effect of unconsciousness at the same rate as an ultra-fast-acting barbiturate.

Based on their carefully extracted phrases from medical literature and expert testimony, defendants attempt to create a narrative that medical minds can differ on the chemical properties of barbiturates and the classifications based thereon, particularly, anesthesiologists. To the contrary, the Court in *Smith v. Montana*, No. BDV-2008-303, 2015 WL 5827252, at *1 (Mont. Dist. Ct. Lewis and Clark County Oct. 6, 2015), cites Margaret Wood and Alistair J.J. Wood's text, "DRUGS AND ANESTHESIA PHARMACOLOGY FOR ANESTHESIOLOGISTS" (2d. ed.,Williams & Wilkins 1989), in support of the statement that "[b]arbiturates are traditionally classified as long-acting (phenobarbital), medium-acting (such as pentobarbital), short-acting (secobarbital), and ultra-short-acting (thiopental)." *Smith*, 2015 WL 5827252, at *2. In their response, Defendants cited an article on neurosurgical anesthesia to support their argument, *see* Response Mot. Prelim. Inj. 14, but that article itself recognizes that pentobarbital is not an ultra-short-acting barbiturate: "[L]ittle is known about the hemodynamic effects of pentobarbital in humans, at least when given in the doses needed for neurosurgical purposes. *This contrasts with the large body of data concerning the effects of the ultrashort-acting anesthetic barbiturates such as thiopental.*"). Todd, Drummond and Sang, Hemodynamic Effects of High Dose Pentobarbital: Studies in Elective Neurosurgical Patients, 20 NEUROSURGERY 559 (1987) (emphasis added).

Other authorities specific to the field of anesthesiology and outside the field of pharmacology likewise classify pentobarbital as a short-acting barbiturate. *See, e.g.*, Helen Lamb, The barbiturates: with particular reference to their use in anesthesia. Bulletin of the American

Association of Nurse Anesthetists. 1943;12(4): 228-29 (identifying pentobarbital as a barbiturate "of moderate duration" while identifying evipal, pentothal, and thio-ethymal as "ultra-short-acting barbiturates"); Torben Seear, Pentobarbital Anesthesia in Labor, M.D. AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Vol. 99, Issue 7, p. 955 (Dec. 1967) ("Pentobarbital is a short-acting, but not ultrashort-acting barbiturate."); Peter D. Bryson, *Comprehensive Review in Toxicology for Emergency Clinicians* 464 (3d. ed. 2018) (classifying Pentobarbital in the "Short – and Intermediate-acting" Barbiturate classification as opposed to the "Ultrashort-acting" classification); Sandra J. Cunningham & Waseem Hafeez, "Procedural Sedation and Pain Management Techniques," Textbook of Pediatric Emergency Procedures 423 (Christopher King & Fred M. Henretig eds., 2d ed. 2008) (identifying pentobarbital as "a short-acting barbiturate," as opposed to methohexital which is an "ultrashort-acting barbiturate").

Further, manufacturers of pentobarbital refer to it as a short-acting barbiturate. Not only does the FDA-approved branded manufacturer's insert for Nembutal Sodium Solution, which is the manufacturer's name for pentobarbital, state: "NEMBUTAL Sodium is a short-acting barbiturate," (Fritz Exh. 4), but the manufacturers for generic pentobarbital, Sagent and Leucadia, similarly state that pentobarbital is a short-acting barbiturate. *See* https://www.sagentpharma.com/wp-content/uploads/2017/11/Pentobarbital_PI-Revised.pdf; http://leucadiapharma.com/wp-content/uploads/2018/02/Pentobarbital_PI_Art_Clean.pdf.

The State repeatedly mischaracterizes testimony on the classification of barbiturates from a different expert, Dr. Mark Heath, in different litigation. Dr. Heath's testimony supports Rhines's position. Dr. Heath used the terms "ultra-short" and "ultra-fast" interchangeably, and he consistently referred to that category of barbiturates in "*contrast*" with pentobarbital. *Compare* State's Exhibit 8 at transcript page 21–22 ("I'll just start by comparing ultra-short and ultra-fast-

acting barbiturates which will enter the brain very quickly in a matter of tenths of seconds, and will also leave the brain very quickly . . . . and those drugs would be the class of drug would be thiopental, for example, and another would be a drug called methohexital."), *with id.* at transcript page 22 ("*By contrast,* pentobarbital is slower to take effect and lasts for longer." (emphasis added)). The State pulls quotations out of context, but even these quotations never establish that this different expert classified pentobarbital as "ultra-short-acting." *See, e.g.*, State's Exhibit 11 at transcript page 90 (explaining that the line dividing ultrafast from fast-acting barbiturates "is really a molecular line. . . . . [Molecular] modifications have created a class unto itself."). The State goes so far as to repeatedly cite the expert's testimony in *Smith*, the very premise of which was that pentobarbital is not an ultra-short-acting barbiturate. Thus, that there are "different ways" to classify barbiturates does not change that Dr. Heath never placed pentobarbital in any sort of "ultra-short" or "ultra-fast" category. *See* State's Exhibit 8 at transcript page 21.

Consistent with this evidence, numerous cases have recognized that pentobarbital is not a short-acting barbiturate. *See McGehee v. Texas Dep't of Criminal Justice*, No. MC H-18-1546, 2018 WL 3996956, at *2 (S.D. Tex. Aug. 21, 2018) ("Testimony in other cases has established that pentobarbital is 'not classified as an ultra-short-acting barbiturate.' *Mann v. Palmer*, 713 F.3d 1306, 1313 (11th Cir. 2013)."); *Bible v. Davis*, No. 4:18-CV-1893, 2018 WL 3068804, at *1 (S.D. Tex. June 21, 2018) ("Pentobarbital is an intermediate-acting barbiturate") (internal quotation omitted), aff'd, 739 F. App'x 766 (5th Cir. 2018); *West v. Schofield*, 519 S.W.3d 550, 553 (Tenn. 2017) (stating that pentobarbital is "described in [Tennessee's execution] Protocol as 'an intermediate-acting barbiturate'") (internal brackets omitted); *Grayson v. Warden, Comm'r, Alabama DOC*, 869 F.3d 1204, 1210 (11th Cir. 2017) (describing "pentobarbital, [as] a short-acting barbiturate sedative") (internal quotation marks omitted); *West v. Warden, Comm'r,*

Alabama DOC, 869 F.3d 1289, 1292 (11th Cir. 2017) (describing "pentobarbital, [as] a short-acting barbiturate sedative") (internal quotation marks omitted); *Whitaker v. Livingston*, No. CV H-13-2901, 2016 WL 3199532, at *1 (S.D. Tex. June 6, 2016) ("Pentobarbital is an intermediate-acting barbiturate."), *aff'd sub nom. Whitaker v. Collier*, 862 F.3d 490 (5th Cir. 2017); *Smith v. Montana*, No. BDV-2008-303, 2015 WL 5827252, *2 (Oct. 6, 2015) ("Barbiturates are traditionally classified as long-acting (phenobarbital), medium-acting (such as pentobarbital), short-acting (secobarbital), and ultra-short-acting (thiopental).") (Exh. A to the Compl.); *Williams v. Com., Dep't of Corr.*, No. 353 M.D. 2014, 2015 WL 6474764, at *5 (Pa. Commw. Ct. Oct. 15, 2015) (considering challenge to inclusion of pentobarbital in execution protocol under statute requiring execution with "an ultrashort-acting barbiturate" and "chemical paralytic agents" and concluding: "taking Petitioners' allegation that pentobarbital and potassium chloride are neither ultrashort-acting barbiturates nor chemical paralytic agents as true, Petitioners have stated a claim that the Protocol violates the statute."); *Trottie v. Livingston*, No. CV 4:14-2550, 2014 WL 12527181, at *2 (S.D. Tex. Sept. 5, 2014) ("pentobarbital . . . is an intermediate-acting barbiturate.") (internal quotation omitted); *Arthur v. Thomas*, 974 F. Supp. 2d 1340, 1345 (M.D. Ala. 2013) ("Sodium thiopental is classified as an 'ultra-short acting barbiturate,' while pentobarbital is an 'intermediate-acting barbiturate.' As these classifications indicate, sodium thiopental has an extremely rapid onset of effect and subsequent recovery, while pentobarbital is slower and longer-acting."); *Arthur v. Thomas*, 674 F.3d 1257, 1274 (11th Cir. 2012) ("sodium thiopental is 'ultrashort-acting,' while pentobarbital is 'intermediate-acting'") (internal quotation and citation omitted); *Powell v. Thomas*, 643 F.3d 1300, 1304 (11th Cir. 2011) ("sodium thiopental is 'ultrashort-acting,' while pentobarbital is 'intermediate-acting'") (internal quotation and citation omitted); *In re Jacoby Airplane Crash Litig.*, No. CIV.99-6073 (HAA), 2007 WL 5037683, at *22

(D.N.J. Aug. 27, 2007) ("The ultrashort-acting barbiturates produce anesthesia within about one minute after intravenous administration.... Barbiturate abusers prefer the Schedule II short-acting and intermediate-acting barbiturates that include amobarbital (Amyta®), pentobarbital (Nembutal®), secobarbital (Seconal®), and Tuinal (an amobarbital/secobarbital combination product).") (internal quotation and citation omitted). Nearly all of these cases arose in the lethal injection context thus belying Defendants' suggestion that pentobarbital's classification changes to ultra-short-acting when it is used in lethal doses for execution.

Defendants cite cases in their response that, they claim, state that there is no difference between sodium thiopental and pentobarbital. As described during the hearing, those cases arose in the context of Eighth Amendment challenges focused on various execution protocols' likelihood to produce unnecessary suffering. not one of them states that pentobarbital is classified as an ultra-short-acting barbiturate, the only issue before this Court. In fact, undersigned counsel is aware of no case that identifies pentobarbital as an ultra-short-acting barbiturate.

The plain language of the statute at issue here is clear. Just as the Court held in the *Smith* case, had the legislature intended to give the State of South Dakota latitude in what drugs to use, it could have used much more general language in the statute authorizing execution. Instead of "ultra-short-acting barbiturate" the legislature could have said "barbiturates in doses that have the effect of ultra-short-acting barbiturates." Courts may not legislate through judicial interpretation of statutes and the Court should not second-guess and substitute its judgment for that of the legislature, or insert what the legislature omitted.

II. As a Matter of Law, This Action Was Timely Brought And The Application Should Not Be Denied on the Basis of Defendants' Equitable Interest in Having Rhines Executed Next Week.

This action was not ripe until weeks ago and was timely brought within the time-frame set forth in SDCL § 23A-27A-32.1. That fact that Rhines was sentenced many years ago or the fact that he has litigated different rights previously over the years is of no consequence here. What matters here is that this action was not ripe until Rhines was informed that the DOC would be using pentobarbital and that he brought it more than seven days prior to his scheduled week of execution.

Whether an issue could have been properly litigated in an earlier action requires consideration of whether the issue actually had been ripe for determination at the time of that earlier action. *See State v. Hammerquist*, 67 S.D. 417, 293 N.W. 539, 541 (S.D. 1940) (declining to apply res judicata, noting "[a]t the time of hearing and decision resulting in the order, *that which was originally conditional had ripened* into an order setting the state's judgment aside" (emphasis added)); *Danforth v. City of Yankton*, 25 N.W.2d 50 (S.D. 1946) ("The case was submitted upon the assumption that there existed a controversy properly determinable under the Declaratory Judgment Law. If there was an absence of jurisdiction in the trial court to consider the questions presented, the declarations are advisory only and would not be res judicata.").

Ripeness involves the timing of judicial review and the principle that the judicial machinery should be conserved for problems that are real and present, not squandered on problems that are abstract, hypothetical, or remote. *Steinmetz v. State, DOC Star Academy*, 756 N.W.2d 392, 399 (S.D. 2008). Courts should not render advisory opinions or decide theoretical questions when the future shows no indication of the invasion of a right. *Id.*; *Boover v. South Dakota Bd. Of Accountancy*, 526 N.W.2d 747, 750 (SD 1995).

Here, Mr. Rhines could not have properly raised this issue in any prior litigation. Prior litigation focused on whether the 2007 statutory amendments and the August 2011 protocol complied with the Eighth Amendment standards as set forth by the United States Supreme Court in *Baze v. Rees*, 533 U.S. 35 (2008). *See* Feb. 27, 2013, Op., Trimble, J.at 8. Judge Trimble determined that the protocol was sufficiently similar to *Baze* that it was constitutional on its face, *id.* at 10–12, and that South Dakota would implement its protocol in a constitutional manner. *Id.* at 12–18.

There were no facts or issues relating to the statute in effect at the time of Mr. Rhines's sentencing or the use of an ultra-short-acting barbiturate. And for good reason. In 2011, there was no reason to believe that the State would not abide by the statutory requirement that, if elected, the state would deliver a lethal dose of an ultra-short acting barbiturate and chemical paralytic agent. The State possessed sodium thiopental, an ultra-short-acting barbiturate, and there was no reason to believe that the State would not use that drug in compliance with the statutory mandate.

Thus, at the time of the prior litigation, there was no concern that the State would choose to disregard the statutory mandate. The issues became ripe on October 17, 2019, when, in response to Mr. Rhines's election within the statutory timeline and under an active warrant, the State announced that it would use pentobarbital instead of the mandated ultra-short-acting barbiturate. Prior to that date, any issue concerning the use of pentobarbital in place of an ultra-short-acting barbiturate would have been speculative, abstract, and remote, and not the subject of judicial review. Res judicata does not apply.

Dated this 30th day of October, 2019.

BALLARD SPAHR LLP

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STATE OF SOUTH DAKOTA	)	IN CIRCUIT COURT
	:SS	
COUNTY OF MINNEHAHA	)	SECOND JUDICIAL CIRCUIT

CHARLES RUSSELL RHINES, Plaintiff, v. SOUTH DAKOTA DEPARTMENT OF CORRECTIONS, MIKE LEIDHOLT, SECRETARY, SOUTH DAKOTA DEPARTMENT OF CORRECTIONS, AND DARIN YOUNG IN HIS CAPACITY AS WARDEN OF THE SOUTH DAKOTA STATE PENITENTIARY, Defendants.	CIV. 19-002940 **THIS IS A CAPITAL CASE EXECUTION SET FOR BETWEEN NOVEMBER 3, 2019 AND NOVEMBER 9, 2019**

AFFIDAVIT OF DANIEL R. FRITZ

STATE OF SOUTH DAKOTA)
:SS
COUNTY OF MINNEHAHA)

Daniel R. Fritz, being first duly sworn on oath, states and alleges as follows:

1. I am an attorney for Plaintiff Charles Russell Rhines in the above-captioned case, and I have knowledge of the matters herein.
2. Attached hereto as Exhibit 1 is a true and correct copy of selected pages from 1 Lawyers' Guide to Medical Proof § 106.02 (2019).
3. Attached hereto as Exhibit 2 is a true and correct copy of selected pages from 9 Attorneys Textbook of Medicine (Third Edition) P. 51.10 (2019).
4. Attached hereto as Exhibit 3 is a true and correct copy of selected pages from Peter D. Bryson, Comprehensive Review in Toxicology for Emergency Clinicians (3d. ed. 2018).

5. Attached hereto as Exhibit 4 is a true and correct copy of selected pages from Francisco López-Muñoz, et al., The History of Barbiturates a Century After Their Clinical Introduction, NEUROPSYCHIATRIC DISEASE AND TREATMENT, Vol. 1(4) (Dec. 2005).

6. Attached hereto as Exhibit 5 is a true and correct copy of selected pages from Torben Seear, Pentobarbital Anesthesia in Labor, M.D. AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, Vol. 99, Issue 7 (Dec. 1967).

7. Attached hereto as Exhibit 6 is a true and correct copy of selected pages from Linda Lilley, et al., Pharmacology and the Nursing Process (9th ed. 2020).

8. Attached hereto as Exhibit 7 is a true and correct copy of selected pages from PHARMACOLOGY (Richard A. Harvey & Pamela C. Champe eds.) (4th ed. 2009).

9. Attached hereto as Exhibit 8 is a true and correct copy of selected pages from Sandra J. Cunningham & Waseem Hafeez, "Procedural Sedation and Pain Management Techniques," Textbook of Pediatric Emergency Procedures 423 (Christopher King & Fred M. Henretig eds., 2d ed. 2008).

10. Attached hereto as Exhibit 9 is a true and correct copy of selected pages from Carl Burtis et al., Tietz Textbook of Clinical Chemistry and Molecular Diagnostics 1325-26 & Table 34.10 (4th ed. 2006).

11. Attached hereto as Exhibit 10 is a true and correct copy of selected pages from Subcommittee on Anesthesia of National Research Council, Fundamentals of Anesthesia: An Outline 38 (American Medical Association Press 1942).

Dated this 30th day of October 2019.

Daniel R. Fritz

Subscribed and sworn to before me this 30th day of October, 2019.

(SEAL)

JUDY L. DECKER
Notary Public
SEAL
South Dakota

Notary Public – South Dakota

3/7/24

EXHIBIT 1

1 LAWYERS' GUIDE TO MEDICAL PROOF § 106.02

LAWYERS' GUIDE TO MEDICAL PROOF > PART 1 HOW THE LAWYER MUST LOOK AT MEDICINE: A BASIC ORIENTATION > CHAPTER 106 Pharmaceutical Drugs and Medical Devices

§ 106.02 Glossary of Prescription and Non-Prescription Drugs

-A-

Abacavir Sulfate. The FDA approved this drug in September 2008. It sold under the trademark Ziagen®, and is used in combination with other antiretroviral medications to treat HIV-1 infection. Abacavir Sulfate belongs to the class of drugs known as nucleoside reverse transcriptase inhibitors. The following reactions may indicate allergy or hypersensitivity to Abacavir Sulfate: skin rash, fever, nausea, vomiting, diarrhea, severe fatigue, severe achiness, sore throat, dyspnea, cough, pharyngitis or shortness of breath. If these symptoms are ignored, more severe symptoms may follow sometimes within hours, including life-threatening low blood pressure and death. This drug can also cause a condition called lactic acidosis, which, together with an enlarged liver, can be fatal. Because resistance to the HIV virus can occur quickly with single-drug treatment, Abacavir should be taken in combination with other antiretroviral medications and should never be taken alone to treat HIV.

Acetaminophen. Acetaminophen (N-acetyl-p-aminophenol; APAP; paracetamol) was clinically introduced in 1955 and has since become the most widely used over-the-counter analgesic-antipyretic in the United States. The drug is indicated for a wide variety of arthritic and rheumatic conditions involving musculoskeletal pain, as well as other painful disorders such as headaches and menstrual cramps. Acetaminophen is also recommended for the discomfort, common cold fevers, and other viral infections.

Lay people commonly underestimate acetaminophen's toxicity. For decades the drug was thought rarely to produce any side effects except for liver toxicity in patients who take excessive doses for an extended period of time. In 2001, however, researchers at the University of Texas Southwestern Medical Center in Dallas released a report suggesting that overdoses of acetaminophen could pose a greater risk of liver failure than several other prescription drugs that were removed from the market due to rates of liver toxicity.

Many consumers are unaware that many prescribed and over-the-counter medications contain some amount of acetaminophen thereby increasing the risk of accidental overconsumption of the drug. In March 2014, in effort to reduce the risks of inadvertent acetaminophen overdose, the FDA issued Federal Register notices that formally withdrew applications for all prescription drugs containing more than 325mg of acetaminophen per tablet, capsule, or other dosage unit. Manufacturers of previously approved products that contain more than 325mg discontinued marketing for those products while any pending applications for approval were voluntarily withdrawn in compliance with the FDA's request (FDA, 2014).

Acetaminophen with Codeine, Hydrocodone, Propoxyphene, or Oxycodone. Acetaminophen (e.g., Tylenol®) with codeine is used to treat mild to severe pain. Some of the side effects are constipation, nausea, drowsiness, anxiety, difficulty breathing, palpitations, rash, fever and sore throat, unusual bleeding or bruising and jaundice. Extreme drowsiness may result if taken with alcohol, antihistamines, barbiturates, Benzodiazepine tranquilizers, or tricyclic antidepressants. Liver damage may occur when taken with anticonvulsant drugs, barbiturates, and alcohol. Some individuals self-administer of acetaminophen with codeine to get "high." The product, therefore, should be kept away from individuals that have a history of substance abuse.

Acetazolamide. This drug, sold under the trade names Diamox® and Sequels®, is used to treat glaucoma, epilepsy and edema. Its major side effects may include back pain, black tarry stools, blurred vision, convulsions, difficulty urinating, fever, rash, jaundice or unusual bleeding or bruising, upset stomach, vomiting, and loss of

occur in elderly patients. Occasional hypersensitivity reactions have been observed, especially skin rashes which in some instances progressed to exfoliation.

Azathioprine (Azasan, Imuran). Patients are prescribed Azathioprine to protect against rejection of transplanted organs and to treat severe, active rheumatoid arthritis and other immunologic diseases. Possible adverse reactions include rapid heart rate, sudden fever, muscle or joint pain, cough, shortness of breath, infection or low blood count causing fever and chills, back pain, cough, painful urination, anemia, vomiting, appetite loss, jaundice, low platelet count causing bleeding or bruising, tarry or black stools, bloody urine, red spots under the skin, severe abdominal pain and mouth sores.

Use of azathioprine with other drugs may have severe consequences, especially allopurinol (increasing azathioprine activity), clozapine (potentially causing a toxic effect on bone marrow), tiopronin (increasing the risk of toxicity to bone marrow), immunosuppressants (increasing the risk of infection or malignancies), and vaccines (potentially decreasing effectiveness of vaccine or cause the disease itself).

Azathioprine may increase the risk of developing certain types of cancer, especially skin cancer and lymphoma (cancer that begins in the cells that fight infection). In kidney transplant patients, there may be a higher risk of developing cancer even for patients who do not take azathioprine. Azathioprine can cause a decrease in the number of blood cells in the bone marrow, which may cause serious or life-threatening infections. That risk is highest in patients who have a genetic (inherited) risk factor.

Azithromycin (Zithromax, Zmax). Azithromycin is an antibiotic used for respiratory tract infections and sexually transmitted diseases. Its major side effects include fever, palpitations, rash, swelling of the neck or face, jaundice, and shortness of breath. Azithromycin interacts with aminophylline, theophylline, carbamazepine, cyclosporin, phenytoin, digoxin, triazolam, phenobarbital, ergotamine, dihydroergotamine and blood thinners. Use with antacids decreases its effectiveness.

A 2012 study reported an increased number of cardiovascular-related deaths as well as an increased risk of death from unknown causes among individuals that were treated with a 5-day course of azithromycin (Zithromax) compared to individuals treated with amoxicillin or ciprofloxacin (Ray, et al., 2012).

-B-

Balsalazide (Colazal). The FDA approved Balsalazide in July 2000 under the brand name Colazal®. Balsalazide, is used to treat ulcerative colitis, a condition in which the bowel is inflamed. Balsalazide is an anti-inflammatory drug. It is converted in the body to mesalamine and works by reducing bowel inflammation, diarrhea, rectal bleeding, and stomach pain.

Side effects from balsalazide can occur such as: headache, abdominal pain, upset stomach, diarrhea, vomiting, joint pain, difficulty falling or staying asleep, tiredness, gas, runny nose, muscle or back pain, coughing, loss of appetite, urinary tract infection, constipation, or dry mouth. More serious side effects include yellowing of skin or eyes, dark urine, stomach bloating or swelling, increased diarrhea, rectal bleeding, fever, sore throat, or flu-like symptoms.

Barbiturates. Barbiturates are a class of drugs prescribed in low doses to reduce anxiety, nervous tension, or to aid sleep. Barbiturates produce a wide spectrum of central nervous system depression, from mild sedation to coma, and have been used as sedatives, hypnotics, anesthetics, and anticonvulsants. The primary differences among many of these products are how fast they produce an effect and how long those effects last. Barbiturates are classified as ultrashort, short, intermediate, and long acting. Higher dosages are used to reduce the likelihood of seizures in persons with epilepsy. An overdose of barbiturates may cause deep sleep, difficulty breathing, coma and weak pulse.

In rare cases, barbiturates may cause agitation, slow heartbeat, difficulty breathing, jaundice, and chest pain. Other more common side effects include unexplained bleeding or bruising, dizziness, drowsiness, "hangover," rash or

hives on face or lip and eyelid swelling, sore throat, fever, depression, confusion, diarrhea, nausea, vomiting, joint or muscle pain, slurred speech, hallucinations and headache.

The ultrashort-acting barbiturates produce anesthesia within about one minute after intravenous administration. Those in current medical use are the Schedule IV drug methohexital (Brevital®), and the Schedule III drugs thiamylal (Surital®) and thiopental (Pentothal®). Barbiturate abusers prefer the Schedule II short-acting and intermediate-acting barbiturates that include amobarbital (Amytal®), pentobarbital (Nembutal®), secobarbital (Seconal®), and Tuinal (an amobarbital/secobarbital combination product). Other short and intermediate-acting barbiturates are in Schedule III and include butalbital (Fiorinal®), butabarbital (Butisol®), talbutal (Lotusate®), and aprobarbital (Alurate®). After oral administration, the onset of action is from 15 to 40 minutes, and the effects last up to six hours. These drugs are primarily used for insomnia and preoperative sedation. Veterinarians use pentobarbital for anesthesia and euthanasia.

Long-acting barbiturates include phenobarbital (Luminal®) and mephobarbital (Mebaral®), both of which are in Schedule IV. Effects of these drugs are realized in about one hour and last for about 12 hours, and are used primarily for daytime sedation and the treatment of seizure disorders.

Belladonna. Belladonna is used to reduce spasms of the digestive system, bladder and urethra. Possible adverse reactions or side effects include confusion, delirium, rapid heartbeat, nausea, vomiting, decreased sweating, constipation, rash or hives, eye pain, blurred vision and lightheadedness.

Use with other drugs may increase or decrease the effectiveness of belladonna. Although widely regarded as unsafe, belladonna is used as a sedative, to stop bronchial spasms in asthma and whooping cough, and as a cold and hay fever remedy. It is also used for Parkinson's disease, colic, motion sickness, and as a painkiller.

Benazepril (Lotensin®). Benazepril (Lotensin®) is an angiotensin-converting enzyme (ACE) inhibitor designed to treat high blood pressure. The drug may be contraindicated in patients who are allergic to other ACE inhibitors, as well as patients who have: (1) kidney disease (or who are on dialysis); (2) liver disease; (3) heart disease or congestive heart failure; (4) diabetes; or (5) a connective tissue disease such as Marfan syndrome, Sjögren's syndrome, lupus, scleroderma, or rheumatoid arthritis.

Also, patients should not use this medication without informing their physician if they are pregnant or planning to get pregnant, since the drug can cause birth defects if taken during pregnancy. It can also pass into breast milk and may harm a nursing baby.

Benzodiazepines. Benzodiazepines are a class of drugs used to treat seizure disorders, muscle spasms, nervousness and tension. They may also be prescribed for insomnia. Overdose may result in stupor or coma. Normal doses have side effects that include slow heartbeat, breathing difficulty, hallucinations, confusion, depression, irritability, rash, itchiness, vision changes, dry mouth, sore throat, fever, chills, vivid dreams, behavior changes, abdominal pain and headache. Use of Benzodiazepines in conjunction with other drugs may increase the effects of other drugs, possibly with dangerous results. For example, use with tranquilizers increases the tranquilizer's effect and may dangerously slow down the heartbeat. Use with other anticonvulsants may change the type and severity of seizure activity.

Short-acting benzodiazepines are generally used for patients with sleep-onset insomnia (difficulty falling asleep) without daytime anxiety. Shorter-acting benzodiazepines used to manage insomnia include estazolam (ProSom®), flurazepam (Dalmane®), temazepam (Restoril®), and triazolam (Halcion®). Midazolam (Versed®), a short-acting benzodiazepine, is utilized for sedation, anxiety, and amnesia in critical care settings and prior to anesthesia. It is available in the United States as an injectable preparation and as a syrup (primarily for pediatric patients).

Benzodiazepines with a longer duration of action are utilized to treat insomnia in patients with daytime anxiety. These benzodiazepines include alprazolam (Xanax®), chlordiazepoxide (Librium®), clorazepate (Tranxene®), diazepam (Valium®, halazepam (Paxipam®), lorazepam (Ativan®), oxazepam (Serax®), prazepam (Centrex®), and quazepam (Doral®). Clonazepam (Klonopin®), diazepam, and clorazepate are also used as anticonvulsants.

Author

Roger Cicala, M.D.
and
Robert Liebman

¶ 58.10 GENERAL ANESTHESIA

In providing general anesthesia during a surgical procedure the anesthesiologist is responsible for rendering the patient unconscious and relieving pain. In addition, an important function of the anesthesiologist is to maintain the patient's hemodynamic stability.

General anesthesia involves not only a loss of consciousness but also produces amnesia for the procedure. Either intravenous or inhalation agents can be used for general anesthesia. Often intravenous agents are used for induction of anesthesia because they act very quickly and inhalation agents are used for maintaining anesthesia because they provide better control of the depth of unconsciousness.

Injections of muscle relaxants may be given in order to relax the patient's skeletal muscles which is advantageous in many types of surgical procedures. Also, if a patient needs to be intubated a muscle relaxant is given to facilitate the procedure. Because muscle relaxants paralyze the respiratory muscles, it is critical that before such an agent is given the anesthesiologist is certain that the patient can be adequately ventilated.

During surgery the patient may breathe spontaneously, be assisted with breathing, or have breathing controlled. Breathing can take place either through a mask or an endotracheal (placed inside the trachea) tube. If lengthy controlled breathing is required an endotracheal tube is used and the patient is ventilated mechanically. (*See Figure 58-1.*)

During anesthesia induction and while under anesthesia the patient is carefully monitored. Standards for intraoperative monitoring have been set by the American Society of Anesthesiologists (ASA). One standard requires that when general anesthesia is used someone qualified in anesthesia must be present in the operating room at all times. Another standard requires that a continual evaluation be made of the patient's oxygenation, ventilation, circulation and temperature.

It is extremely difficult to assess the risk of death associated with anesthesia. It is known that the risk is very small, perhaps 1 in 100,000 for a healthy person. The overall mortality appears to be between 1 in 10,000 and 1 in 20,000 (Berthoud and Reilly, 1992). Over the last several decades as improvements in various aspects of anesthesia have occurred the risks have decreased considerably. It is likewise very difficult to assess the risk of serious morbid events associated with anesthesia but such risks are believed to also be very small. On the other hand, potentially serious events requiring intervention by the anesthesiologist do occur.

Although one of the main purposes of general anesthesia is to induce a state of unconsciousness, patients have reported that they were actually aware of what was happening during surgery. In one study of this phenomenon, 26 patients who reported awareness during surgery under general anesthesia were systematically interviewed (Moerman, et al., 1993). The most frequently reported memories were auditory perceptions and the sense of being paralyzed. Many of the patients also reported feeling pain. Feelings of anxiety, panic, powerlessness and helplessness were also commonly reported. Seventy percent of the patients said they had had unpleasant aftereffects such as flashbacks and anxiety during the day and sleep disturbances at night. In another study, 700 patients who underwent surgery involving cardiopulmonary bypass were interviewed postoperatively with regard to their recall of events during the surgical procedure (Phillips, et

cylinders attached to the anesthesia machine. The percentage of each carrier gas in the gas mixture is controlled by flowmeters. The liquid volatile agent is vaporized in a special vaporizer and is added to the carrier gases as they flow through. The process is calibrated so that there is specific volume percent of volatile anesthetic.

The gas mixture is delivered from the anesthesia machine to the patient via a breathing circuit. The most commonly used breathing circuit for adults is known as the circle system. For pediatric patients the Mapleson breathing circuits are used.

The circle system prevents the patient from rebreathing exhaled carbon dioxide, reduces the need for fresh inhalation anesthetic, and keeps the humidity higher. After passing through a chemical absorber in the breathing circuit to remove carbon dioxide, exhaled gases are allowed to pass into the scavenging system which delivers waste gases to a vacuum system. The remaining exhaled air is rebreathed along with freshly delivered gas.

Mapleson breathing circuits do not have an absorber to remove carbon dioxide. In these types of breathing circuits expired gas is washed out by the flow of fresh gas.

The patient may be allowed to breathe spontaneously, if able to, or ventilation may be assisted by compression of the reservoir bag on the anesthesia machine to direct gases into the lungs. Ventilation may also be controlled by a mechanical ventilator. Determination of whether ventilation is adequate is done by auscultation (listening with a stethoscope) of breathing sounds, and checking the reservoir bag or ventilator, and the monitors that are being used. Arterial blood gas analysis may also be needed.

An adequate depth of anesthesia to permit surgery is determined by the application of noxious stimuli. If a painful stimulus does not cause voluntary muscle reflexes or adverse autonomic responses such as hypertension, the depth of anesthesia is considered to be adequate.

The depth of anesthesia should not become too light or too deep. With inadequate anesthesia the patient may respond to surgical stimuli with movement. If the anesthesia is too deep, the patient may exhibit shallow or no respiration, dilated pupils that are not reactive and low blood pressure which may progress to circulatory collapse. If the depth of anesthesia is determined to be too deep steps should be taken immediately to lighten it.

[58.15] Intravenous Anesthetics

The intravenous anesthetics include barbiturates, narcotics, ketamine, benzodiazepines, etomidate and propofol. They are usually used for the induction of general anesthesia. In some cases these agents may be used for maintenance of general anesthesia, either alone or in combination with inhalation agents. When used for maintenance anesthesia these drugs may be given as a steady infusion or as repeated boluses.

[1] Barbiturates

The barbiturates that are given for anesthesia are classified as ultrashort-acting. Specific barbiturates that are used include thiopental, thiamylal and methohexital. These drugs produce anesthesia very quickly as unconsciousness occurs about half a minute after injection. They act fast because they immediately enter the bloodstream and soon thereafter reach the brain. Inhalation anesthetics act much more slowly because they have to be absorbed through the alveoli to enter the bloodstream. Recovery from barbiturate anesthesia is quick and takes about five to ten minutes.

The dosage of barbiturates for anesthesia induction is usually based on the patient's weight. However, lower doses than normal should be given under special circumstances.

Extreme care must be taken when giving barbiturates intravenously to be sure that the drug does not infiltrate tissues outside of the vein or enter an artery. Severe pain or tissue damage can result because these agents are very alkaline.

Barbiturates should not be given to patients who have had an allergic reaction to a barbiturate. Also, barbiturates are contraindicated in patients who are believed to be at increased risk for porphyria (metabolic disturbances involving porphyrin, a chemical structure that is part of hemoglobin and some other molecules).

[2] Narcotics

Narcotics are not actually total anesthetics because their primary effect is analgesic. Therefore they are most often used as supplements to true anesthetics. In some circumstances, however, when given in high doses they may be used alone for anesthesia.

The narcotics that are frequently used in general anesthesia are morphine, meperidine, fentanyl, alfentanil and sufentanil. The latter two drugs are the most recent to be introduced into clinical practice.

Because sufentanil is a particularly potent analgesic, being about five to ten times as potent as fentanyl, it has become widely used for major surgery. It has been found to reduce the stress responses that occur during anesthesia and seems to be superior to fentanyl for postoperative analgesia (Isaacson, 1992).

Alfentanil, which is only about one fourth as potent as fentanyl, has a particularly short duration of action. Because its effects do not last long it is often used in the ambulatory surgical setting.

Narcotics can cause severe postoperative respiratory and central nervous system depression. However, this can be reversed by a narcotic antagonist, usually the drug naloxone. Because naloxone reverses the effects of narcotics, including the analgesic effects, a patient may experience pain as well as accompanying hemodynamic alterations after it is administered.

[3] Ketamine

Ketamine is an anesthetic that is generally used for induction. Unlike other intravenous agents which cause cardiovascular depression and decreased peripheral resistance with a resulting decline in cardiac output, hypotension, and increase in heart rate, ketamine stimulates the cardiovascular system. Ketamine results in an increase in arterial pressure, cardiac output and heart rate. Ketamine can be given intramuscularly as well as intravenously. This drug produces what is known as a dissociative anesthesia, which means that during recovery from ketamine anesthesia the patient may have vivid and disturbing dreams (Berthoud and Reilly, 1992). The incidence of this phenomenon has been reported to be as high as 30 percent. Only very rarely, however, do these disturbances result in prolonged psychological problems.

[4] Benzodiazepines

Benzodiazepines are generally used as supplementary drugs in general anesthesia but they may also be used for anesthesia induction. These agents produce sedation and amnesia. They have very little analgesic effect. When benzodiazepines are given with narcotics, care must be taken to avoid excessive respiratory depression. There are three benzodiazepines that are used in general anesthesia: diazepam, lorazepam and midazolam. The first two drugs are given orally or via the intravenous route, while midazolam may be given either intravenously or intramuscularly.

The effects of benzodiazepines can be reversed by using the benzodiazepine antagonist flumazenil (Hoffman and Warren, 1993). Flumazenil can reverse sedation, respiratory depression and amnesia. However, since flumazenil has a relatively short half-life resedation may occur after the initial dose. Therefore, in some cases, additional doses may be required.

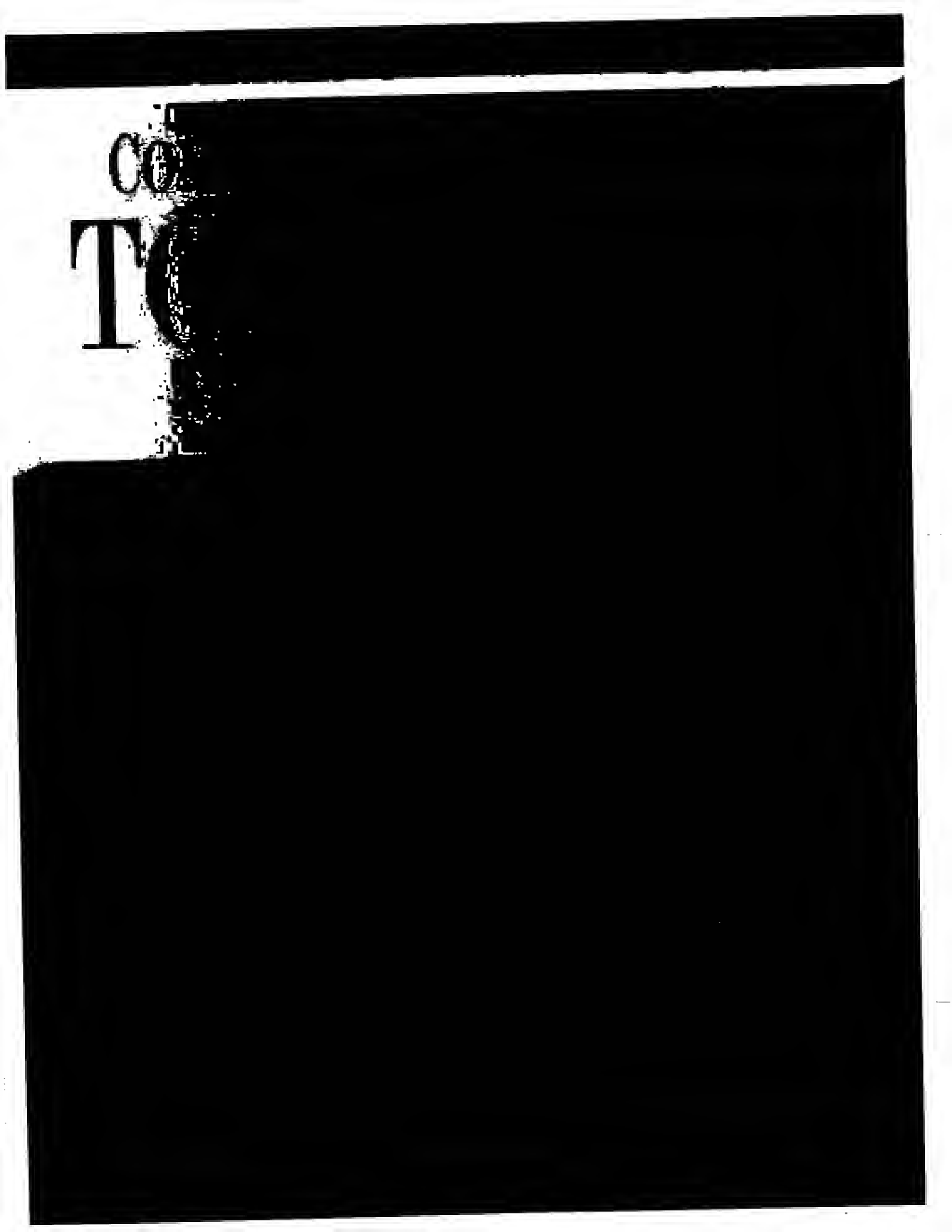
[5] Etomidate

Etomidate is an intravenous anesthetic that is most often used to induce general anesthesia. Etomidate is classified as a hypnotic (a drug that induces sleep). It does not have analgesic properties. Because its effects on the cardiovascular system are minimal it is often preferred for inducing anesthesia in patients with hemodynamic instability.

[6] Propofol

Propofol is an intravenous anesthetic that became available for clinical use in the United States in 1989. It is used for both anesthesia induction and maintenance and is classified as a sedative/hypnotic (Deegan, 1992). Propofol depresses the central nervous system as well as the cardiovascular and respiratory

EXHIBIT 3



Comprehensive Review in *Toxicology* for Emergency Clinicians

Third Edition

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TABLE 47–1. *Classification of barbiturates by duration of action*

Ultrashort-acting
Thiopental
Methohexital
Buthalital
Hexobarbital
Thiamylal
Short- and intermediate-acting
Amobarbital
Aprobarbital
Butabarbital
Butalbital
Pentobarbital
Secobarbital
Talbutal
Long-acting
Phenobarbital
Mephobarbital
Metharbital

elimination is primarily by metabolic degradation or excretion, and the rate of removal of the active drug from the central nervous system. On the basis of these differences in the duration of action, barbiturates are classified into three categories: ultrashort-acting, short- and intermediate-acting, and long-acting (Table 47–1) (1). The anticonvulsant primidone (Mysoline) is metabolized to phenobarbital and thus should be considered a barbiturate (4).

Following oral administration, the onset of action varies from 10–30 minutes for amobarbital, aprobarbital, butabarbital, pentobarbital, and secobarbital and from 20–60 minutes for metharbital, mephobarbital, and phenobarbital. There appears to be little difference in duration of the hypnotic action among barbiturates used orally as hypnotics (9). For this reason, barbiturates have recently been grouped according to their intended pharmacologic action, sedative-hypnotic or anesthetic, rather than according to the duration of their action, since classification problems also arose when it was found that the length of time that the drug action persisted did not parallel the time it took to eliminate half the dose of the drug, the elimination half-life. Although the old classification is not used, nothing has been devised to replace it. However, because of the convenience of categorizing barbiturates as to their duration of action, this method is used in this chapter.

The fatal dose of barbiturates with intermediate or short half-lives is usually lower than the fatal dose of drugs with longer half-lives. For example, to induce severe poisoning, it takes less pentobarbital than phenobarbital when they are compared on a milligram-to-milligram basis (3).

Ultrashort-Acting Barbiturates

The ultrashort-acting barbiturates are thiopental, methohexital, buthalital, hexobarbital, and thiamylal (10). These drugs are not a source of abuse, and there should be no occasion to see an overdose with these drugs in an emergency department setting.

Short- and Intermediate-Acting Barbiturates

The short-acting and intermediate-acting barbiturates, such as secobarbital and pentobarbital, are used for induction of general anesthesia. Their relatively swift onset and short duration of action allow for general anesthesia that is rapid and easily reversible. Ease of titration and low acute toxicity in usual doses add to their usefulness (7).

The short- and intermediate-acting barbiturates have an onset of action of 15–40 minutes and a duration of 6 hours. These drugs are the most widely used and abused barbiturates, both separately and in combination. They include, among others, pentobarbital, secobarbital, amobarbital, and butalbital (Table 47–2). Tuinal is a combination of amobarbital and secobarbital and is a favored drug for abuse. Overdoses of the short acting barbiturates have the highest mortality rate (4,11).

Long-Acting Barbiturates

The long-acting barbiturates have an onset of action of approximately 1 hour and a duration of action of up to 16

TABLE 47–2. *Selected trade names of commonly abused barbiturates*

Amobarbital
Amytal
Aprobarbital
Alurate
Butabarbital
Butal
Butalan
Butapan
Butatran
Buticaps
Butisol
Sodubarb
Butalbital
Fiorinal
Mephobarbital
Mebaral
Pentobarbital
Nembutal
PBR/12
Phenobarbital
Luminal
Phen-Bar
Sedadrops
Secobarbital
Seconal
Talbutal
Lotusate

EXHIBIT 4

The history of barbiturates a century after their clinical introduction

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Abstract: The present work offers an analysis of the historical development of the discovery and use of barbiturates in the field of psychiatry and neurology, a century after their clinical introduction. Beginning with the synthesis of malonylurea by von Baeyer in 1864, and up to the decline of barbiturate therapy in the 1960s, it describes the discovery of the sedative properties of barbital, by von Mering and Fischer (1903), the subsequent synthesis of phenobarbital by this same group (1911), and the gradual clinical incorporation of different barbiturates (butobarbital, amobarbital, secobarbital, pentobarbital, thiopental, etc). We describe the role played in therapy by barbiturates throughout their history: their traditional use as sedative and hypnotic agents, their use with schizophrenic patients in so-called "sleep cures" (Klaesi, Cloetta), the discovery of the antiepileptic properties of phenobarbital (Hauptmann) and their use in the treatment of epilepsy, and the introduction of thiobarbiturates in intravenous anesthesia (Lundy, Waters). We also analyze, from the historical perspective, the problems of safety (phenomena of dependence and death by overdose) which, accompanied by the introduction of a range of psychoactive drugs in the 1950s, brought an end to barbiturate use, except in specific applications, such as the induction of anesthesia and the treatment of certain types of epileptic crisis.

Keywords: barbiturates, history of medicine, sedative-hypnotic drugs, "sleep cures", epilepsy, anesthesia

Introduction

Throughout the history of humanity, numerous therapeutic agents have been employed for their hypnotic and/or sedative properties, though the true effectiveness of many of them has been fairly limited (Alamo et al 1998). It suffices to mention alcohol itself (in different forms, such as hydromel or wine) or the alkaloids of opium and other narcotic plants (hemp, jimsonweed, belladonna, henbane, etc). More recently, around the late 19th and early 20th centuries, agents such as paraldehyde, chloral hydrate, and bromides were used, until the discovery, at the beginning of the 20th century, of the sedative and hypnotic properties of barbiturates, thanks to the prior synthesis of malonylurea by Adolf von Baeyer in 1864.

The clinical introduction of barbiturates begun a century ago (1904) when the Farbwerke Fr Bayer and Co brought onto the market the first agent of this type, diethyl-barbituric acid, giving rise to profound changes in the pharmacological approach to the psychiatric and neurological disorders of the time. A large number of previously untreatable patients gained access to treatment and improved their prognosis. The most significant results were obtained in the treatment of patients with serious neuroses and psychoses and with severe emotional repression, who as a result of being administered barbiturates, especially intravenously, overcame their inhibitions, thus facilitating psychotherapeutic treatment. Barbiturates were also useful in the treatment of sleep disorders as well as being the first truly effective

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pharmacological tools for the management of epileptic seizures. Furthermore, they opened up the field of intravenous anesthesia, playing a prominent role in anesthetic induction, above all for minor operations.

In the course of the 20th century, more than 2500 barbiturates were synthesized, 50 of which were eventually employed clinically. Their use was widespread and many still have some use today. One hundred years after the introduction in clinical pharmacology of the original compound, oxybarbiturates, in general, continue to be the selected drugs in the treatment of some serious forms of insomnia and in some types of epilepsy. Similarly, some thiobarbiturates and some ultrashort-acting barbiturates are still used today as inducers of general anesthesia. Nevertheless, currently, 5 or 6 derivates of barbiturates are sufficient to cover the therapeutic applications that still require them.

Sedative and anticonvulsant drugs in the pre-barbiturate era

Although, as mentioned, the therapeutic agents historically employed for their sedative, hypnotic, or anticonvulsant effects have been quite numerous, the most specific drugs in this regard have their origin in the 19th century. Such is the case of choral hydrate, different alkaloids and, above all, bromides (Hollister 1983; Sneader 1985; Scott 1992; Lehmann 1993; Shorvon and Sander 1996; Shorter 1997; Alamo et al 1998; Healy 2002).

The second half of the 19th century is called by some authors, such as Shorter (1997), the "alkaloids era". Alkaloids were introduced into psychiatry as sedatives and hypnotics, thanks to the isolation of morphine from opium, in 1805, by the German pharmacist Friedrich Sertürner. In 1861, Wilhelm Griesinger, in the second edition of his *Die Pathologie und Therapie der Psychischen Krankheiten*, defended the use of opium in sleep disorders, pointing out the improvements it brought about in patients suffering from anxiety. However, the alkaloids that met with most success were those isolated from different species of the *Solanaceae* family: plants known for their hallucinogenic effects, such as hyoscyamus, whose sedative and hypnotic properties were described by the Viennese pharmacologist Karl Schroff in 1868. In 1839, chemists at the E Merck company in Darmstadt (Germany) had already isolated hyoscyamine, another alkaloid, which became popular in the late 19th century, forming part of many of the "cocktails" administered in neuropsychiatric institutions at that time (Woodward 1994). Finally, the year 1880 saw the isolation of hyoscine (called scopolamine in North America), an alkaloid that was also widely used in psychiatric cocktails, such as the famous Hyoscine Co A, which contained hyoscine, morphine, and atropine, and was administered to highly excited and aggressive manic patients (Norton 1979).

The first drug that could truly be called hypnotic is chloral hydrate. Synthesized in 1832 by Justus von Liebig, a chemist from Giessen, it was not analyzed as a hypnotic until 1869 by the Berlin pharmacologist Oskar Liebreich. The hypothetical mechanism to which its action was ascribed was based on the mistaken belief that, in vivo, chloral hydrate was capable of transforming itself into formic acid and chloroform, whose properties were already known at that time (Sourkes 1992). Very soon, chloral hydrate substituted morphine and the *Solanaceae* alkaloids, given its convenience, as it could be administered without the need for injection, allowing treatment in the home and making it unnecessary to confine patients to neuropsychiatric institutions (Shorter 1997).

Nevertheless, it would be the bromides that were most widely used in the second half of the 19th century, either as sedatives or for the treatment of epilepsy, having been introduced for these applications by the internist and obstetrician Sir Charles Locock in 1857. It was in that year that Locock reported his results in the treatment with bromides in women with what the author has named as catamenial or hysteriform epileptic seizures, obtaining positive outcomes in 14 women out of a sample of 15. From that time on, bromides were widely introduced in asylums and similar institutions throughout Europe, given their sedative and antiepileptic properties, the relevant function in the latter case being to reduce the expression of the epileptic patients' sexuality. Another contribution in relation to the neuropsychiatric use of bromides was made by the British doctor Neil MacLeod, who in 1897, while working in Shanghai, carried out the first "sleep cure" with these salts. MacLeod called it "the bromide sleep" (MacLeod 1900), and some authors, such as Shorter (1997), have considered this technique as the first pharmacological therapy that, within psychiatry, succeeded in improving the symptoms of psychiatric patients. However, the main problem with bromides resided in their high toxicity (neurological and gastrointestinal disorders, irritability, hallucinations, deliria, and lethargy), given their long half-life (elimination taking around 12 days) and their capacity for accumulation in tissue; as a result, they were gradually phased out after the introduction of barbiturates in the early part of the 20th century (Balme 1976).

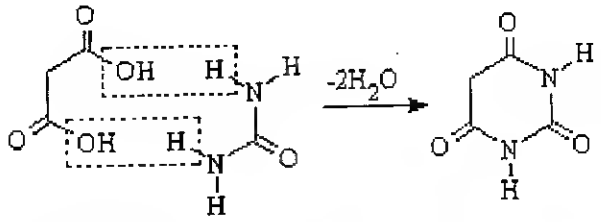

Figure 1 Synthesis of barbituric acid, from the combination of malonic acid (left) and urea (right).

Other substances used as hypnotics and sedatives and eventually as anticonvulsants were also introduced in the 19th century and the early decades of the 20th century. Such is the case of paraldehyde, discovered by Wildenbusch in 1829 and introduced into clinical practice by Vincenzo Cervello in 1882; and sulphonal, whose hypnotic action was discovered by chance by Eugen Baumann and Alfred Kast in 1887 (Kast 1888). Finally, those seeking to treat epilepsy turned, as well as to potassium bromide, chloral hydrate, or hyoscine, to a whole host of substances of more questionable efficacy, including opium, belladonna, atropine, stramonium, strophanthus, *cannabis indica*, and zinc oxide.

The discovery and clinical introduction of barbiturates as sedative and hypnotic agents

Between the 1920s and the mid-1950s, practically the only drugs used as sedatives and hypnotics were barbiturates (Lehmann and Ban 1970). From a chemical point of view, these drugs are closed-chain ureic compounds, whose nucleus is malonylurea (a combination of urea, a product present in animal excrement, and malonic acid, an acid derivative taken from apples) (Figure 1). Barbiturates were synthesized in 1864 by Adolf von Baeyer, though the synthetic process was developed and perfected by the French chemist Edouard Grimaux in 1879, making possible the subsequent widespread development of barbiturate derivatives (Carter 1951). Von Baeyer, a disciple of Robert W Bunsen and Friedrich A Kekulé, taught at the universities of Strasbourg and Munich, was the founder of what was to become the Bayer Chemical Co, and received the Nobel Prize in Chemistry in 1905 for his contribution to the development of organic chemistry (Figure 2a).

There are various hypotheses about the origin of the term "barbiturates" (Dundee and McIlroy 1982). According to one of these, Baeyer may have used this name for the compounds for sentimental reasons, in honor of his friend Barbara (Cohen 1943). Other authors, however, claim that the name derives from the fact that Baeyer celebrated his discovery in a tavern near his home that was frequented by artillery officers, who themselves were celebrating the day of their patron, St Barbara (Sharpless 1970). A third possibility is that the term is inspired by the "barbed" appearance of the crystals of these ureic compounds (Fieser 1944). In any case, it is clear that the union of the elements "barb(ara)" and "urea" forms the basis of the name.

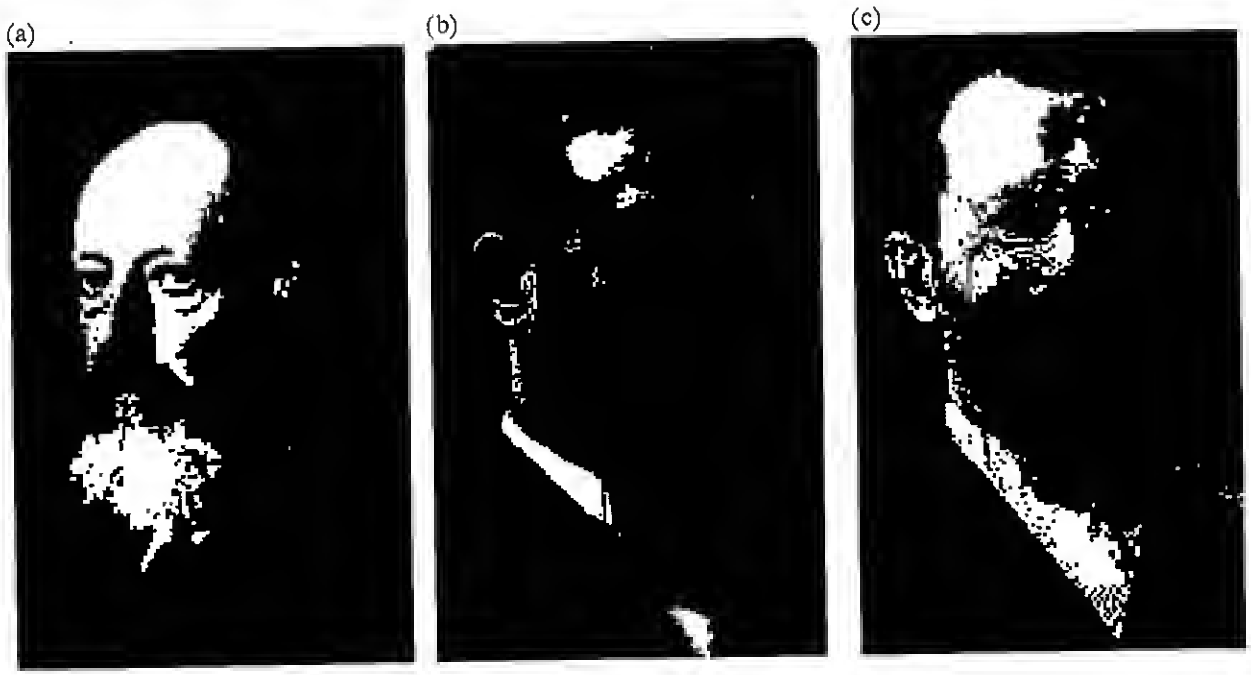

Figure 2 (a) Adolf von Baeyer (1835–1917); (b) Josef von Mering (1849–1908); (c) Emil Fischer (1852–1919).

From malonylurea to barbital

The first of the barbiturates to come onto the market was diethyl-barbituric acid, also known as barbital, malonal, or gardenal. Synthesized in 1881 by Conrad and Guthzeit, on treating the argentic salt of barbituric acid with ethyl iodide, it was introduced clinically as a hypnotic by the German companies E Merck (Darmstadt) and F Bayer and Co (Elberfeld) in 1904, thanks to the work of Josef Freiherr von Mering (Figure 2b) and Emil Fischer (Nobel Prize in Chemistry, 1902) (Figure 2c).

Von Mering, who taught pharmacology at the University of Halle, had observed that some of the synthetic compounds obtained towards the end of the 19th century and commercialized as hypnotics, such as sulphonal, contained in their molecular structure a carbon atom with two ethyl groups. Furthermore, knowing of von Baeyer's work with derivatives of urea, von Mering decided to study the hypnotic properties of diethyl-acetylurea, and found that it was even more potent than sulphonal. The next step was to analyze the properties of 5,5-diethyl-barbituric acid, for which he turned to Fischer, an old friend from his student days. At that time, Fischer, doyen of the German organic chemists, was Professor of Chemistry at the University of Berlin. Moreover, Fischer was well acquainted with the chemistry of malonylurea, as he had been von Baeyer's assistant in Munich for eight years. Together with his nephew Alfred Dilthey, he tested the new, resynthesized product, demonstrating, in dogs, that its hypnotic power was far greater than that of von Mering's diethyl-acetylurea (Sneader 1985). When Fischer told his friend von Mering about this finding, the latter happened to be in the Italian city of Verona, and it was this that prompted him to call the new drug Veronal® (Cohen 1943; Sharpless 1970). Nevertheless, other authors argue that the name Veronal (from Latin, verus=true) was coined by Fischer, who claimed to have found the "true" hypnotic compound (Sneader 1985). This new hypnotic drug was patented by Fischer in January 1903, and two months later the first scientific data on barbiturates were published in a brief report (Fischer and von Mering 1903). The licence for its commercialization in the USA was granted to the Winthrop Chemical Company.

The term barbital for diethyl-barbituric acid is a later development, coming as a result of the economic effects of World War I. After the United States entered the conflict, in 1917, Congress passed the Trading with the Enemy Act 1917, which permitted them as a kind of war booty to manufacture German products protected by patent, modifying their generic name and with the profits going to the American subsidiaries of the German companies (Sneader 1985). Thus, the American Medical Association approved the name barbital, whilst in the United Kingdom, through a similar mechanism, diethyl-barbituric acid came to be called barbitone. From this point on the two endings "-al" and "-one" could be found in the nomenclature of barbiturates.

Veronal had hypnotic, sedative, and anticonvulsant properties (Figure 3a). It could calm manic patients and help melancholic patients to sleep, and was an effective inducer of sleep in insomniacs. The first trials with barbital were carried out by Hermann von Husen (1904), a young psychiatrist affected by sleep disorders, who tried the new drug on himself. After taking 0.5 g of Veronal the first night and 1 g the following night, he reports:

> In both cases, after 10–15 minutes, I felt into a growing state of dejection that led to deep sleep after around 30 minutes. After half a gram of Veronal I slept for 8 hours, and after a whole gram, around 9 hours. On the first morning I awoke fresh and rested; on the second morning, after the higher dose, I found it difficult to get out of bed (von Husen 1904, p 59).

The consolidation of barbiturate therapy: phenobarbital

By means of small modifications to the chemical structure of the barbituric acid molecule, more than 2500 different agents were synthesized. The first barbital analogs, numbering around 18, were synthesized and tested by the group made up of von Mering, Fischer, and Dilthey. One of them, perhaps that most widely used subsequently, was phenobarbital, synthesized by Hörlein in 1911, on substituting one of the ethyl groups by a phenyl radical. Phenobarbital was employed in therapy as a hypnotic for the first time in 1912 by Loewe, Juliusburger, and Impens, and that same year it was commercialized by F Bayer and Co, under the name Luminal®. Phenobarbital, with a more prolonged pharmacological action than its predecessor, soon became "king of the barbiturates", both in hospitals and in outpatient care (Shorter 1997). This drug opened up the way, moreover, to another important therapeutic application of barbiturates, as will be mentioned later: the treatment of epilepsy.

Both Veronal (barbital) and Luminal (phenobarbital), the first two representatives of the series of barbiturates, were accepted by the international pharmacopoeia, such as the *United States Pharmacopoeia* (USP X) in 1926, and the *British Pharmacopoeia* in 1914 and 1932, respectively.

Later, both drugs were also included in the *Pharmacopoeia Internationalis*.

Clinical introduction of the new barbiturates

The new barbiturates brought substantial advantages compared with their classical predecessors, such as a greater potency and duration of action, as well as a wider therapeutic range. However, of the several thousand that were synthesized, only about 50 came onto the market, and of these no more than a couple of dozen were regularly used in clinical practice. The next barbiturate to be used successfully in therapy was butobarbital, whose history begins in World War I. The British war effort required large quantities of acetone for the manufacture of explosives (Sneader 1985), and one of the solutions was provided by Chaim Weizmann, who would later become the first president of the state of Israel. Weizmann found that the bacteria *Clostridium acetobutylicum* was capable of transforming materials rich in starch into acetone and butyric alcohol, and at low industrial cost. After the war, the cost of butyric alcohol, a chemical that was as useful as it was expensive, fell drastically, thus permitting its use for obtaining numerous synthetic drugs. In 1920, Roger Adams (Abbott Laboratories, Chicago, USA) synthesized the ester of 5-butyl-5-ethyl-malonic acid, an intermediate stage in the synthesis of a butyl analog of barbital, which was finally synthesized by Arthur Dox (Parke Davis and Company, Detroit, USA) in 1922, and marketed the following year by Abbott Laboratories, under the name Neonal® (Sneader 1985). Butobarbital (butethal in the USA) was three times as strong as barbital and its period of action was much shorter due to its lipophilicity, which greatly lowered the possibility of "rebound" drowsiness the day after administration.

In the years that followed, new barbiturates continued to come onto the market. In 1923, it was amobarbital (Amytal®), synthesized by Shonle and Moment (Eli Lilly Company, Indianapolis, USA) by adding a carbon atom to the butyl chain of butobarbital; and in 1929, Horace A Shonle also synthesized secobarbital (Seconal®). Both barbiturates had quite similar pharmacological properties to those of butobarbital (Sneader 1985). The next drugs of this series to be introduced were pentobarbital (Nembutal®), synthesized by Volwiler and Tabern (Abbott Laboratories) in 1930, and thiopental (Pentothal®). The latter, a sulfur derivative of pentobarbital, presented at the American Chemical Society congress in San Francisco in August 1935 (Tabern and Volwiler 1935), would revolutionize intravenous

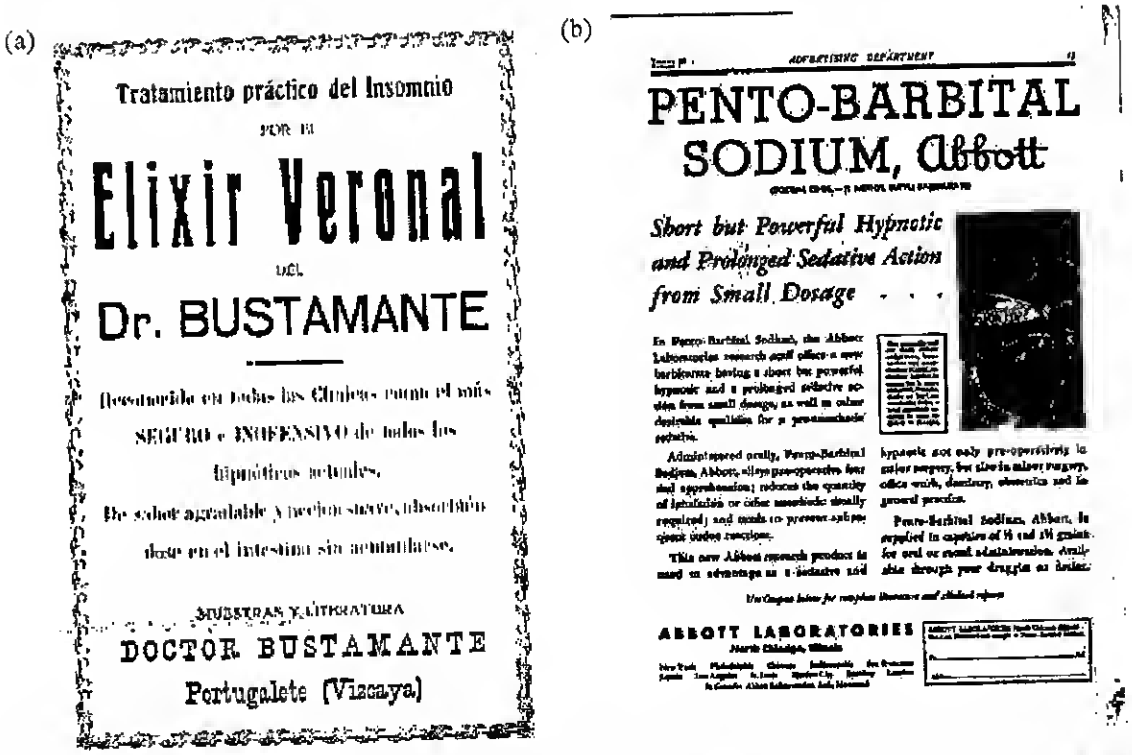

Figure 3 (a) Elixir Veronal from Dr Bustamante's Laboratories it is a "Practical treatment of insomnia". They have also added audaciously "Secure and harmless". Finally they say that "It tastes good and acts smoothly, being absorbed by the organism". (b) Advertisement for Abbott sodium pentobarbital in an American medical journal of 1933, highlighting its "short but powerful hypnotic effect and prolonged sedative action from small dosage".

Table 1 Mean and maximum dosage of the pharmacological agents used as hypnotics before the benzodiazepine era

Drug	Dosage per administration		Daily maximum dosage
	Mean dosage	Maximum dosage	
Ethchlorvynol	250mg	500mg	750mg
Chloral hydrate	500mg	1000mg	1000mg
Paraldehyde	3mL	8mL	8mL
Glutethimide	250mg	500mg	500mg
Methyprylon	200mg	400mg	400mg
Methaqualone	200mg	400mg	600mg
Phenobarbital	50–100mg	200mg	200mg
Amobarbital	50–100mg	200mg	200mg
Secobarbital	100mg	200mg	200mg
Pentobarbital	100mg	200mg	200mg
Sodium tripental	250mg	500–1000mg	–

NOTE: The doses indicated correspond only to the hypnotic use of these drugs. The maximum doses of the barbiturates are not considered when they are used as anticonvulsants.

anesthesia and would be the only representative of the thiobarbiturate family to be officially recognized, being accepted first by the *British Pharmacopoeia* (1942, 7th Add) and subsequently by the *United States Pharmacopoeia* (1947, USP XIII) and the *Pharmacopoeia Internationalis* (1951, Volume I). Figure 3b shows an advertisement for pentobarbital in an American journal of the time.

Table 1 shows the recommended dosages of barbiturates used as hypnotics together with those of other drugs also used as hypnotics prior to the clinical introduction of benzodiazepines at the end of the 1950s. Among these last agents, chemically different from barbiturates although with similar pharmacological actions, we have to mention glutethimide (USV Pharmaceutical Corporation, 1954), methyprylon (Hoffmann-La Roche, 1955), methaqualone (King George Medical College, Lucknow, India, 1956; William H Rorer Inc, 1965), chlormethiazole (Hoffmann-La Roche, 1956), and ethchlorvynol (Pfizer, 1956). Most of these drugs were introduced as barbiturate substitutes, due to the fact that they seemed to offer a wider margin of safety. However, the clinical experience has demonstrated that their addiction liability and the severity of withdrawal symptoms were similar to those of barbiturates, and most of them were removed from the market some years later.

The role of barbiturates in "sleep cures" for schizophrenic patients

The hypnotic properties of some barbiturates were rapidly applied to the treatment of psychotic patients, thanks to their induction of a state of deep and prolonged sleep. The pioneer of these techniques was the Italian psychiatrist Giuseppe Epifanio, working at the University Psychiatric Clinic in Turin, who described his technique in an article published in 1915. The lack of impact of this development on the international scientific community can be attributed to the fact that it was published only in an Italian journal, and in the middle of the Great War (Epifanio 1915). It was on 25th March 1913 that Epifanio administered the first dose of Luminal to a girl aged 19 (FL) affected by manic-depressive psychosis, extending the treatment over a period of 4 days. The patient fell into a "deep sleep" that lasted until 9th April, was discharged at the end of June, and was in remission during the next two years. This case marked the beginning of what Manfred Bleuler would describe in 1955 as "the first of the great physical therapies" for mental disorders (Windholz and Witherspoon 1993).

However, the clinical introduction of these techniques is historically associated with Jakob Klaesi, a psychiatrist at the University Psychiatric Clinic in Zurich (Psychiatrische Universitätsklinik, Burghölzli, Switzerland). His "sleep cures" ("Dauerschlaf", "Dauemarkose"), proposed in 1920 within the framework of the 59th Assembly of the Swiss Psychiatry Society (28th November 1920), enjoyed great prestige at the time and directly involved the use of barbiturates. Klaesi's initial proposal was that his techniques for inducing deep hypnosis, taken from Epifanio, would facilitate communication between patient and psychotherapist ("to achieve a better relationship between doctor and patient") (Shorter 1997, p 204). Klaesi introduced his method in Switzerland, and based it on pre-medication with morphine (0.01 mL) and scopolamine (0.001 mL) and the subsequent administration (intravenous or subcutaneous), over at least 6–7 days, of Somnifen® (Figure 4), a mixture of diethyl and dipropenyl-barbituric acid and diethylamine (2–4 mL), manufactured by the Hoffmann-LaRoche company. The percentage improvements reported by Klaesi, in samples of schizophrenic patients, ranged from 25% to 33%, which is 10% higher than the rates of spontaneous remission in this type of patient (Klaesi 1922). These cures ("prolonged sleep therapy") acquired great popularity during the 1920s, with numerous variations as regards methodology and applications (agitated schizophrenic patients, delirium tremens, autism, morphine dehabituation, etc), though the administration of Somnifen was always involved (Windholz and Witherspoon 1993). Nevertheless, it is important to consider a fact mentioned in the first publication on the effectiveness of the method in schizophrenic patients: three of the 26 patients recruited died during the study due to

Figure 4 The packaging of Somnifen®, produced by Hoffmann-LaRoche.

bronchopneumonia or hemorrhages in the cardiac muscles (Klaesi 1922). A few years later, some authors set the mortality rate with Somnifen at around 5% (Müller 1927).

The legacy of Somnifen was taken up at the same Swiss clinic in Burghölzli by pharmacologist Max Cloetta and psychiatrist Hans W Maier, who sought a compound that would be better tolerated. In 1934, they prepared a compound based on paraldehyde, amylen hydrate, chloral hydrate, alcohol, ephedrine hydrate, digalen, and isopropyl-allyl-barbituric acid, which they called Cloettal® or "Cloetta Mixture", and which was rectally administered (Cloetta and Meier 1934). This preparation was widely used in schizophrenic patients, not only in the Zurich clinic (Boss, Monnier), but also elsewhere, such as in the Soviet Union by Ivan P Pavlov (Windholz and Witherspoon 1993). The most rigorous study with this mixture was carried out in Burghölzli by Marcel Monnier, who, with a sample of 125 schizophrenic patients, applied strict exclusion criteria (elderly patients and those with renal or respiratory disorders) before applying the preparation. Only 84 patients were given the Cloetta Mixture, and 53 of them improved (40 were even discharged from the hospital). Nevertheless, two patients died during the treatment as a result of respiratory complications associated with the medication (Monnier 1936).

Eliot Slater, of the Maudsley Hospital in London, recalled that "sleep cures" were "the only treatment we had back in the 1930s that was of any value in acute psychotic disorders" (Slater 1975, p 74). After this initial period, the use of "sleep cures" based on barbiturates began to decline due in part to problems of safety, as well as to the clinical introduction of new biological therapies for the treatment of schizophrenic patients such as Sakel's (1935) insulin shocks or the cardiazolic shocks of von Meduna (1937). Even so, as Shorter (1997) points out, "the story of barbituric narcosis has a corollary". This refers to the work of D Ewen Cameron in the mid-1950s at the Psychiatry Department of the Allan Memorial Institute in Montreal (Canada). Financed by the Central Intelligence Agency (CIA), Cameron developed his technique of "psychic driving" (Cameron 1956), a prototype version of what would come to be known commonly as "brainwashing". With this technique, in which barbiturates were also used, Cameron intended to take advantage of prolonged sleep to force his patients to listen to propaganda messages, which, in this case, were designed to quicken their recovery. In spite of its aims, eminently clinical, this work was widely criticized in the mass media at the time.

Barbiturates as antiepileptic agents

With phenobarbital, in addition to confirmation of the excellent hypnotic effect of barbiturates, it was demonstrated that these drugs had significant anticonvulsant properties. The discovery of these properties took place in 1912, the year of their commercialization, and provided another example of serendipity in the field of psychopharmacology. Alfred Hauptmann, resident psychiatrist in Freiburg, was given responsibility for the care of epileptic inpatients. Finding it impossible to sleep properly because of the continual convulsive seizures of his patients, Hauptmann decided to administer them some of the new hypnotics on the market, among them phenobarbital. Surprisingly, Hauptmann observed that the incidence of seizures in patients treated with low doses of phenobarbital fell notably, not only during the night, but also during the day (Hauptmann 1912). One of Hauptmann's most important conclusions was that phenobarbital not only reduced the number of seizures, but also their intensity, allowing many patients to leave the institutions and enjoy a normal working life.

It was in this way that the anticonvulsant properties of barbiturates were discovered, phenobarbital being the first truly effective drug for the treatment of epilepsy (Iváñez and Díez-Tejedor 1998). Table 2 shows, by way of example,

Table 2 Anticonvulsant drugs used at the National Hospital (Queen Square) in London, before and after the clinical introduction of phenobarbital in the treatment of epilepsy

1910		1930	
Drugs of definite benefit	Drugs of doubtful benefit	Drugs of definite benefit	Drugs of doubtful benefit
Bromides	Monobromate of camphor	Bromides	Zinc salts
Chloral hydrate	Eosinate of sodium	Bromide combinations	Iron
Glycerophosphates	Chloretone	**Phenobarbital**	Digitalis
Borax	Antipyrin	Borax	Strophanthus
Belladonna		Double tartrate of borax and potassium	Calcium
Zinc salts		Belladonna	Opiates
Opium		Nitroglycerine	Hypnotics
Strychnine			
Chloride of calcium			
Atropine			

Adapted from Shorvon and Sander (1996).

the anticonvulsant agents commonly employed in the treatment of epilepsy before and after the introduction of phenobarbital.

However, the international acceptence of phenobarbital as an antiepileptic drug was seriously delayed, due first of all to the scarce significance outside Germany of the journal in which Hauptmann published the reports of his work (*Münchener Medizinische Wochenschrift*), and secondly, to the outbreak of World War I. Indeed, phenobarbitone was not commercialized in Great Britain until 1923, by the Winthrop Chemical Company. In one of his first reports on the use of phenobarbitone in England, Charles Brooks, Colony Medical Officer at the Chalfont Centre in London, noted its particular efficacy in severe cases of convulsions and in epileptic conditions with associated mental deficiency. Brooks also mentioned that if the barbiturate did not show a certain degree of effectiveness in the first months of treatment, the result of the therapy would not be satisfactory, so that it would be necessary to find an alternative (Brooks 1922). In a later report, Brooks made a close examination of patterns of use of phenobarbitone, concluding that it was more effective than bromides, but that it was not particularly useful in patients with low-intensity seizures (Brooks 1923).

It was precisely the Chalfont Centre that published, at the end of the 1920s, one of the first therapeutic guides for newly admitted epileptic patients, written by F Haward (Shorvon and Sander 1996). According to this guide, potassium bromide was the first-choice treatment, though it should be substituted by phenobarbital if there was no remission in the seizures within a given period of time (Table 2). If after three months of treatment the improvement was not clear, the guide recommended treatment with a combination of Luminal® and potassium bromide. Moreover, it set down the recommended dosage for phenobarbitone: 1 grain (65 grams) in the morning and another at night for adult patients, and 1/2 grain in the case of children; the dose was to be increased gradually, according to the clinical response, but should never exceed 6 grains per day (Haward 1928). At the beginning of the 1930s, the use of phenobarbital superseded definitively that of bromides in the treatment of epileptic seizures, despite the first reports of pharmacological tolerance and the risk of seizures when withdrawal was too abrupt. Phenobarbital is currently the most widely-prescribed antiepileptic drug in the world (Shorvon 2000), even though in the developed countries it has passed onto a secondary plane in therapy, for the treatment of partial and generalized seizures, due to its profile of adverse effects.

In the years following the discovery of the antiepileptic properties of phenobarbital, there were studies of numerous barbiturate derivatives in the field of epilepsy, the most important being mephobarbital (Prominal®) (Weese 1932) and, above all, deoxybarbital or primidone (Mysoline®). Primidone was synthesized by Bogue and Carrington (Imperial Chemical Industries Ltd, ICI, Manchester, UK) in 1949, demonstrating its antiepileptic activity in patients with generalized seizures in 1952 (Handley and Stewart 1952). Initially, primidone awoke great therapeutic interest, as it was thought that its anticonvulsant effectiveness may be greater than that of other available barbiturates, and without sedative effects (Bogue and Carrington 1953), but this interest soon waned after it was demonstrated that phenobarbital was a metabolite of this drug, together with phenyl-ethyl-malonamide (Butler and Waddell 1956). Comparative clinical studies carried out with phenobarbital and its prodrug, primidone, showed no differences between

the two (Oleson and Dam 1967). Currently, primidone is still considered as being of some use in partial and secondary generalized seizures, but is not a first-choice drug. Unlike phenobarbital, it cannot be used in epileptic status, since no galenic formulation has been developed for its parenteral administration.

The discovery by Houston Merritt and Tracy Putnam (Boston City Hospital, USA) in 1938 of the anticonvulsant properties of phenytoin (the first drug to show that an antiepileptic need not be a hypnotic), in 1944 of trimethadione, and in the late 1950s of carbamazepine, extended the spectrum of antiepileptic drugs, resulting in decreased use of barbiturates in these applications.

Figure 5 The packaging of Abbott Pentothal® at the time of its clinical introduction in the late 1930s. Pieces from the Museum of the Buenos Aires Anaesthesiology Association (Argentina).

The use of barbiturates in intravenous anesthesia

Despite the existence of some publications on the use of Somnifen® as a general anesthetic as early as 1921 by the French anesthetist Daniel Bardet – who noted that his patients woke up very slowly and with serious headaches (Bardet 1921) – the first barbiturate to be used systematically in anesthesia was sodium sec-butyl-(2-bromo-allyl)-barbiturate (Pernocton®). This was introduced into the field by the German obstetrician Bumm in 1927 (Bumm 1927). Subsequently, as new barbiturates were synthesized for their oral administration as sedatives, sodium salts of the same drugs were formulated, which could be administered intravenously and used as anesthetics (Dundee and McIlroy 1982). Notable among the pioneers in this field is John S Lundy of the Mayo Clinic (Rochester, USA), who introduced sodium amobarbital (1929) and sodium pentobarbital (1930) in anesthesia.

The addition of a methyl group to the butobarbital molecule, by the chemists Kropp and Taub at Bayer (IG Farbenindustrie, Leverkusen) in the early 1930s, gave rise to hexobarbital, whose sodium salt (Evipal®), introduced into clinical anesthesia in 1932 (Weese and Scharpff 1932), constituted the first barbiturate agent that induced anesthesia. Ten years after its introduction, more than 10 million people had undergone operations with the help of this drug (Adams 1944). The duration of hexobarbital's action was shorter than that of its predecessors, given its greater lipophilicity, but under its effect some muscular movements occurred. This problem was solved through the next modification of the chemical structure of the basic nucleus of the barbiturates, the addition of a sulfur group to pentobarbital. Thus born were the agents that would revolutionize intravenous anesthesia, the thiobarbiturates, thanks to the work of Volwiler and Tabern of Abbott Laboratories (Tabern and Volwiler 1935). These agents were studied as anesthetics at the Mayo Foundation (Rochester) by John Lundy's group, who gave the sulfur derivative of pentobarbital the name Thionembutal®. Its sodium salt was marketed as Pentothal (Figure 5). The team led by Ralph M Waters at the University of Wisconsin Medical School (Madison, USA) were the first to begin clinical administration of Pentothal, and published their results in 1936 (Pratt et al 1936). This agent rapidly displaced the rest of the barbiturates as an anesthetic, partly due to the swiftness of its onset and its short action period, and it currently remains the preferred intravenous anesthetic in many types of surgical intervention. Despite the anesthetic efficacy of both hexobarbital and thiopental, the barbiturates most commonly employed in surgery in the mid-20th century, they were not without their clinical problems. Such problems were brought to the public eye in particularly unfortunate fashion after the involvement of these agents, apparently due to malpractice, in numerous cases of death in patients treated in states of shock after the Japanese attack on Pearl Harbor in December 1941. Some authors went as far as describing these drugs as providing the "ideal form of euthanasia" (Halford 1943).

After World War II the search for anesthetic barbiturates continued, and new compounds such as thiobutobarbital (Horatz and Stürtzbecher 1952) were introduced, though the only one that truly challenged thiopental was methohexital (Brietal®), developed by SM Chemish's group at Lilly Research Laboratories (Indianapolis, USA) in 1956. In clinical trials, methohexital showed itself to be more potent than thiopental and to lead to quicker recovery in patients; it was recommended for use as an anesthetic

inducer in minor outpatient surgery (Taylor and Stoelting 1960). The subsequent development of other anesthetic agents for intravenous administration (hydroxydione, alphaxalone, etomidate, propofol, etc) led to a reduction in the use of barbiturates in this context.

The peak and decline of barbiturate therapy

As mentioned earlier, chemists from different universities and pharmaceutical companies managed to synthesize over 2500 barbiturate derivates. The differential pharmacokinetic properties of these agents made it possible to draw up a practical clinical classification, based on the duration of their pharmacological action (Hollister 1983). Thus, the barbiturates in the category of short or intermediate action (secobarbital, amobarbital, pentobarbital) were employed initially as hypnotics, whilst those of prolonged action (phenobarbital) were widely used as anxiolytics and anticonvulsants; ultrashort-acting agents, notably sodium thiopental, were especially useful as anesthetic inducers for minor operations (Table 3). From time to time, some barbiturates have been used in the treatment of other disorders. One such case is the use of primidone in the management of essential tremor (Koller et al 2000), while another is that of combinations of barbiturates and analgesics (salicylates, codeine, etc) in the treatment of headaches, migraines, and other types of pain (Wolf et al 1941), though such applications are considered counterproductive today.

Some barbiturates, such as sodium amytal and sodium pentothal (the latter being known as "the truth serum") were widely known and used as coadjuvant agents for the exercise of narcoanalysis, as initially developed by Bleckwenn in 1930 (Bleckwenn 1930a, 1930b). In principle, the application of an infusion of barbiturates reverted temporarily the catatonic state of certain schizophrenic patients. These cures for catatonia allowed patients, for a few hours, to maintain conversations and interact with their environment, before returning to their state of lethargy. Despite the fact that the response was somewhat brief, these cures were quite customary in European asylums in the 1930s and 1940s. But a variety of this technique became widespread during and after World War II: it consisted of the intravenous administration of a short-acting barbiturate, which had a disinhibiting effect (potentiating positive transfers) and facilitated the subsequent exercise of psychotherapy (a phenomenon referred to as "cathartic abreaction") (Lehmann 1993). This technique was also called by other authors the "induced crepuscular method".

It was during the 1930s and 1940s that barbiturates attained their greatest popularity and were most widely used, putting them in a position that could be compared, according to Hollister (1983), to that currently held by benzodiazepines. The barbiturates most commonly used at that time were phenobarbital, sodium amobarbital, sodium secobarbital, sodium pentobarbital, and sodium thiopental. Despite their widespread use during the first half of the 20th century, no barbiturate succeeded in eliminating the main drawbacks of these drugs, which were the phenomena of dependence and death by overdose (Johns 1977). Among the paradoxes of destiny is the possible death through overdose of the two scientists who introduced the first barbiturate, Fischer and von Mering, after some years of dependence upon these substances (Escohotado 1996). To reduce these problems, from a legal perspective, a series of laws were passed aimed at regulating the distribution and sale of barbiturates. The first of these came into force in California in 1929. However, its effects were limited, if we consider, for example, that the production of barbiturates in the USA increased by more than 400% from 1933, with some 70 tons of these drugs sold in 1936. The problem continued during the following decade, and it became necessary to arrange special conferences for all those involved, such as that held in Washington, under the auspices of the American Pharmaceutical Association, on 12th October 1945 (*Conference on the Regulation of Use and Distribution of Barbiturates*). Barbiturate use in the pre-benzodiazepine period was such that, in the USA alone, production of these drugs reached, in 1955, the quantity

Table 3 Classification and principal clinical applications of the barbiturates most commonly employed before World War II

	Barbiturates	Trade name	Chemical name	Clinical indications
Long-acting	Phenobarbital	Luminal	5-ethyl-5-phenylbarbituric acid	Sedative
Intermediate-acting	Amobarbital	Amytal	5-ethyl-5-isopentylbarbituric acid	Hypnotic
Short-acting	Pentobarbital	Nembutal	5-ethyl-5-(1-methylbutyl)-barbituric acid	Hypnotic and anticonvulsant
	Secobarbital	Seconal	5-allyl-5-(1-methylbutyl)-barbituric acid	Hypnotic
Ultrashort-acting	Thiopental	Pentothal	5-ethyl-5-(1-methylbutyl)-thiobarbituric acid	Anesthesia inducer

Adapted from Hollister (1983).

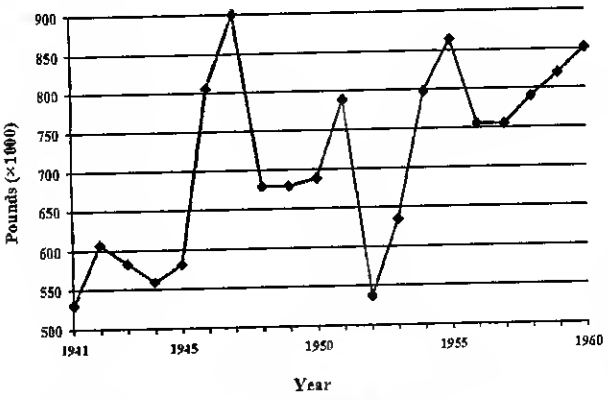

Figure 6 Evolution of annual barbiturates production in USA for the period 1941–1960. Adapted from Fort (1964).

necessary for the treatment of 10 million people throughout an entire year. Figure 6 shows the industrial production of barbiturates and their derivatives in the USA during the 1940s and 1950s.

The capacity of barbiturates to cause dependence was described in the medical literature as early as one year after the commercialization of barbital ("the Veronal habit"), though reliable evidence of the potential of these drugs to generate abuse was not available until the 1950s (Glatt 1962). In fact, doses 4–6 times higher than the therapeutic dose as hypnotics of the short-acting barbiturates (400–600 mg/day of amobarbital, secobarbital, or pentobarbital) brought about, if the treatment was sufficiently prolonged, authentic withdrawal syndromes when use was stopped. In order to palliate these effects, the Narcotics Expert Committee at the World Health Organization recommended (at their sessions of 7th–12th January, 1952, and 18th–24th October, 1956) that barbiturates should only be available on medical prescription. In spite of this, and according to different estimates, in 1965 there were 135 000 barbiturate addicts in England, whilst in the United States it was declared, by a special drug-dependence committee set up by President Kennedy in 1962, that there may be as many as 250 000 Americans addicted to barbiturates. Indeed, the USA currently produces 30 barbiturate pills per inhabitant per year (Escohotado 1996). Some barbiturates (amobarbital and pentobarbital) have even found their way into mixtures with amphetamine derivatives (*goofballs*), such as Dexamyl®, a combination of dextroamphetamine and amobarbital.

In relation to the frequent cases of death by overdose, given the small therapeutic margin of these substances, it should be pointed out that this was a common method in suicide attempts. It suffices to recall, in this regard, the famous case of Marilyn Monroe, on whose death certificate it clearly states "acute poisoning by overdose of barbiturates" (Figure 7). The lethal effect of these compounds was such that a mixture of barbiturates with other substances

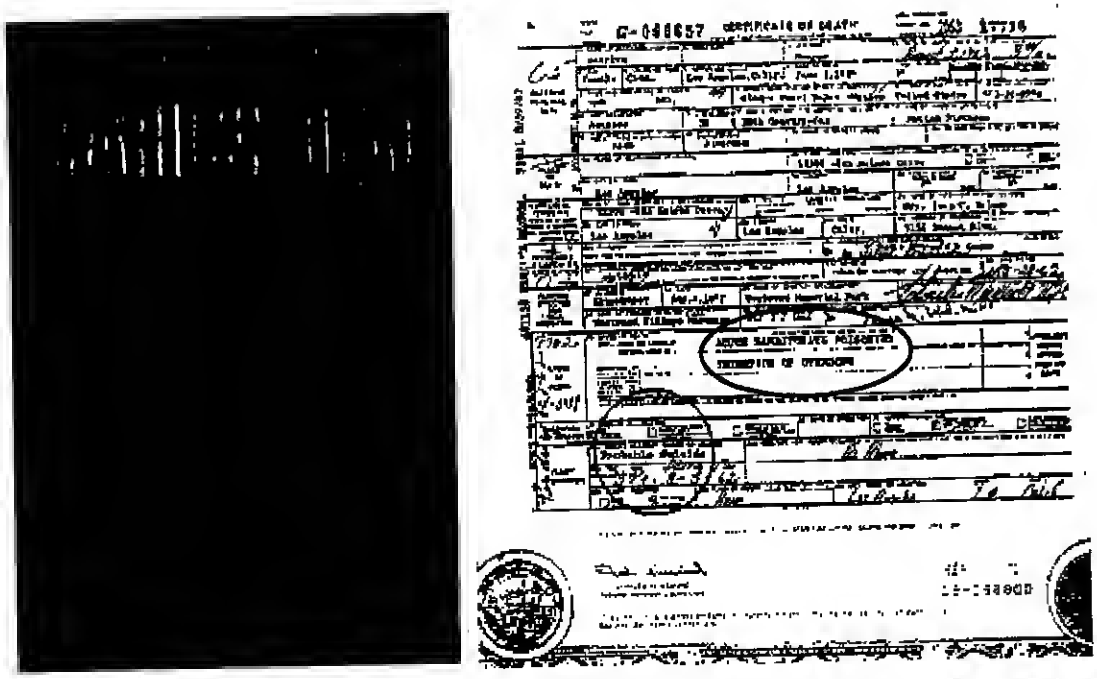

Figure 7 Death certificate of the actress Marilyn Monroe, issued on 28th August 1962. The circles indicate cause of death ("Acute barbiturate poisoning. Ingestion of overdose") and the intentionality ("Probable suicide").

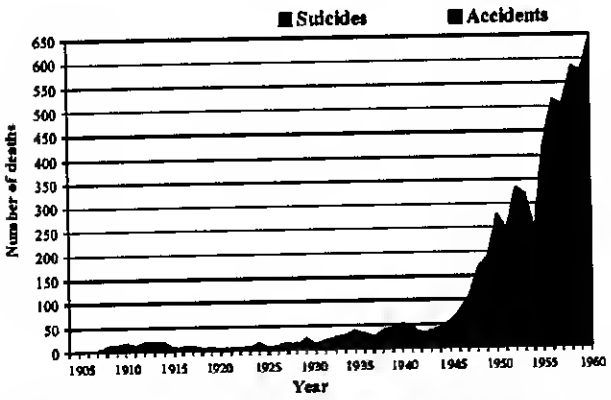

Figure 8 Deaths from overdose of barbiturates in England and Wales during the period 1905–1960 (Registrar-General's Statistical Review for England and Wales). Includes both accidental deaths and suicides. Adapted from Glatt (1962).

was even employed in some USA states for the execution of prisoners sentenced to death. Furthermore, there are classic reports of fatal overdose due to the "automatism phenomenon", whereby the patient would take his or her dose, only to forget that he or she had already taken it, given the amnesic effect of the drug, and take it again, this process being repeated several times (Richards 1934). Figure 8 shows the evolution of number of deaths (accidental or suicide) by barbiturate overdose in England and Wales for the period 1905–1960. In this regard, and in the city of New York alone, in the period 1957–1963, there were 8469 cases of barbiturate overdose, with 1165 deaths (Sharpless 1970), whilst in the United Kingdom, between 1965 and 1970, there were 12354 deaths attributed directly to barbiturates (Barraclough 1974). These data should not surprise us, since in a period of just one year (1968), 24.7 million prescriptions for barbiturates were issued in the United Kingdom (Plant 1981). In view of these data, the Advisory Council Campaign in Britain took measures restricting the prescription of these drugs. Meanwhile, the prescription of prolonged-acting sedative barbiturates was strongly opposed through citizens' action campaigns such as CURB (Campaign on the Use and Restrictions of Barbiturates), especially active during the 1970s.

Furthermore, during the 1950s, when the use of barbiturates was at its peak, there took place a veritable revolution in the approach to psychiatric disorders, thanks to the introduction into clinical practice of the first pharmacological tools aimed specifically at treating these patients (Caldwell 1970; Jacobsen 1986; Ayd 1991; Lehmann 1993; Frankenburg 1994; López-Muñoz et al 2000; Ban 2001; Healy 2002). This "psychopharmacological revolution" began with the discovery and clinical use, from 1952, of chlorpromazine (López-Muñoz et al 2004), culminating in the commercialization of the first benzodiazepine, chlordiazepoxide, in 1960. The discovery of benzodiazepines was actually made possible, in part, by the 60 years of clinical and basic research provided by barbiturates, whose therapeutic life, from that time on, began to decline.

Barbiturates today

Currently, the use of barbiturates is circumscribed to quite specific therapeutic applications (Charney et al 2001). Thus, phenobarbital and butabarbital are still used as sedatives in cases of gastrointestinal and asthmatic functional disorders, as well as to antagonize the adverse central stimulant effects of some drugs, such as ephedrine, dextroamphetamine, or theophylline. Phenobarbital is also used in cases of withdrawal syndromes of hypnosedative agents. In the field of neurology, barbiturates (phenobarbital and primidone) are still employed, not only in the treatment of certain types of epilepsy (partial and tonic-clonic generalized seizures), but also in the emergency treatment of some types of convulsions, such as those associated with tetanus, eclampsia, cerebral hemorrhage, status epilepticus, or different forms of poisoning. As intravenous anesthetic inducers, ultrashort-acting barbiturates are of use, mainly thiopental and methohexital, the latter also being administered rectally in children or as a sedative in some diagnostic imaging explorations. Table 4 shows the therapeutic applications of barbiturates that have survived to the present day.

In addition to these approved indications, the barbiturates present other current uses. Phenobarbital is capable of improving the hepatic transport of bilirubin in patients with hemolytic jaundice, so that it can be used in newborn babies to treat hyperbilirubinemia and kernicterus. At a diagnostic level, amobarbital, in low doses, can be injected directly into the carotid artery prior to neurosurgery to identify the dominant cerebral hemisphere. Finally, anesthetic doses of barbiturates can attenuate post-surgical cerebral edemas and have positive effects in cases of cardiac and cerebral ischemia, reducing the size of the infarcted region. Moreover, barbiturates have been used since the 1970s in the management of acute traumatic brain injury in their capacity to reduce intracranial pressure (Marshall et al 1979). The mechanism through which high-dose barbiturates appear to exert their intracranial pressure-lowering effects is double: reduction of metabolism (with the consequent lower oxygen demand by cerebral tissue)

Table 4 Barbiturates currently employed and therapeutic applications

Barbiturate	Routes of administration	Therapeutic uses
Amobarbital	Oral, IM, IV	Insomnia Preoperative sedation Emergency management of seizures
Aprobarbital	Oral	Insomnia
Butabarbital	Oral	Insomnia Preoperative sedation
Mephobarbital	Oral	Epilepsy Daytime sedation
Methohexital	IV	Induction/maintenance of anesthesia
Pentobarbital	Oral, rectal, IM, IV	Insomnia Preoperative sedation Emergency management of seizures
Phenobarbital	Oral, IM, IV	Epilepsy Status epilepticus Daytime sedation
Primidone	Oral	Epilepsy
Secobarbital	Oral, rectal, IM, IV	Insomnia Preoperative sedation Emergency management of seizures
Thiopental	Rectal, IV	Induction/maintenance of anesthesia Preoperative sedation Emergency management of seizures

Adapted from Charney et al (2001).
Abbreviations: IM, intramuscular; IV, intravenous.

and modifications in vascular tone (Kassell et al 1980). Additionally some direct neuroprotective effects, such as membrane stabilization or inhibition of free radical-mediated lipid peroxidation, have been postulated (Piatt and Schiff 1984). Despite results of the multicenter randomized clinical trial published by Eisenberg et al (1988) that demonstrated the efficacy of high-dose barbiturates in severely head-injured patients with intractable intracranial pressure elevations, recent collaborations, based in Cochrane methodology, concluded that there is no evidence of health improvement in this type of patient (Roberts 2000).

The barbiturates introduced clinically one century ago were the first pharmacological agents to have demonstrated–in an historical period that was therapeutically inhospitable–a real efficacy in different neuropsychiatric disorders. They were the first-line treatment as hypnotics and anticonvulsants during the first half of the 20th century. The clinical results obtained in the last years in other indications such as the treatment (acute or prophylactic) of traumatic brain injury, although contradictory, seems to confirm that, from the pharmacological perspective, the barbiturates continue furnishing certain novelties and that in their history the last page has not yet been written.

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EXHIBIT 5

Pentobarbital anesthesia in labor

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A routine method of balanced obstetric analgesia and anesthesia which can be administered safely by the labor room nurses and the attending physicians is discussed. Eleven thousand eight hundred and twenty patients received intravenous pentobarbital. More than 2,000 of the author's patients received this type of anesthesia. The result of his last 1,000 consecutive anesthetics is discussed in detail. Maternal mortality and morbidity were zero. Corrected stillbirth and neonatal death rates were zero. Obstetric analgesia-anesthesia with the use of meperidine, propiomazine, and pentobarbital seems to be safe and is well accepted.

IN JANUARY, 1847, Sir James Young Simpson administered the first obstetric anesthesia. Ever since then scientists and physicians have worked to improve drugs and methods to make anesthesia better and safer.

Ideally, all obstetric anesthesia should be administered by an anesthesiologist trained in obstetric analgesia and anesthesia. However, only about 500 physicians enter approved anesthesia training programs every year. Shnider[11] found that 40 per cent of the physicians completing a training program in anesthesiology administered fewer than 50 anesthetic agents for vaginal delivery in 2 years, and most anesthesiologists do not order drugs for relief of pain during the first stage of labor.[7]

It has, therefore, been necessary to develop methods of analgesia and anesthesia which can be administered safely by the labor room nurse and the attending physician.

In 1951 Bertling and Burwell[2] published their results regarding pentobarbital anesthesia used routinely since 1948, and in 1953 Flowers[3] recommended balanced analgesia with the use of meperidine, scopolamine, and pentobarbital.

In our community hospital, pentobarbital was given the first time in December, 1951. Meperidine was given as premedication, and ether was used occasionally together with pentobarbital for the delivery. Later, tranquilizers were added, and the use of pentobarbital as the only anesthetic increased gradually, and within a few years it became the predominantly used anesthetic agent (Table I).

From Gaston Memorial Hospital.

Presented by invitation at the Twenty-ninth Annual Meeting of the South Atlantic Association of Obstetricians and Gynecologists, Hot Springs, Virginia, Feb. 5-8, 1967.

Analgesia

Certainly the results of anesthesias, analgesias, and tranquilizers cannot be separated, as all influence the condition of the mother and the newborn. In fact, I feel that it is the development of the new and efficient tranquilizers which have made the use of pentobarbital safer by increasing the analgesic effect of meperidine and the hypnotic effect of pentobarbital causing a smaller total dose of all drugs and, therefore, less risk of depression of the newborn infant. My material has been collected for a little more than 4 years. Promazine was used the first 5 months, propiomazine (Largon) since then (Table II).

The premedication with meperidine, 50 mg., and propiomazine, 40 mg., intravenously is now my preferred treatment. The patients receiving meperidine, 25 mg., and tranquilizers intramuscularly were patients suspected of being candidates for primary uterine inertia or patients in premature labor.

It is my impression that meperidine is

Table I. Number of patients receiving pentobarbital anesthesia

Year	Total cases	Personal cases	Total deliveries
1951	3	0	875
1952	Records not available		
1953	Records not available		
1954	38	1	1,300
1955	133	5	1,375
1956	288	40	1,489
1957	361	64	1,324
1958	674	41	1,345
1959	914	190	1,460
1960	1,206	220	1,457
1961	1,384	233	1,627
1962	1,375	231	1,536
1963	1,388	242	1,524
1964	1,340	229	1,588
1965	1,421	207	1,615
To 10/31/66	1,295	185	1,534
Total	11,820	1,888	20,049

Table II. Frequency of use and dosage of tranquilizers

No. of patients	Drug and dosage	
507	meperidine 50 mg.	propiomazine 40 mg. intravenously
299	meperidine 50 mg.	propiomazine 20 mg. intravenously or intramuscularly
65	meperidine 50 mg.	promazine 25 mg. intramuscularly
129	meperidine 25 mg.	promazine or propiomazine intramuscularly

more depressing to the newborn than pentobarbital; therefore, only 62 patients received additional 25 or 50 mg. of meperidine for analgesia.

Pentobarbital sodium (Nembutal). This solution contains 50 mg. pentobarbital sodium per milliliter in a stable solution. It is strongly alkaline and can only be injected intravenously or deeply into a large muscle.

Pentobarbital is essentially a hypnotic drug, but it also produces a slight degree of analgesia. Following intravenous injection, pentobarbital rapidly produces cerebral depression of any desired degree. It is rapidly detoxified, chiefly in the liver. It transverses the placental barrier easily, and equilibrium between maternal and fetal circulation is reached within 3 minutes.

It has been said about the short-acting barbiturates, that they are "deadly easy to administer." However, if not more than 250 mg. of pentobarbital is given slowly intravenously, it is virtually impossible to oversedate the patient. Pentobarbital may, therefore, be given by a physician or nurse trained in intravenous injection and used to observe and supervise patients in labor.

Method

The patient is given meperidine 50 mg. and a tranquilizer intravenously when labor is established. As the effect of the premedication begins to wear off, the patient is given pentobarbital intravenously.

It is important to know that the dosage is determined by the clinical response of each patient. Approximately 100 mg. pentobarbital is first given slowly. The effect is observed for a couple of minutes before the remainder of the desired dose is given, bearing in mind that full effect is first obtained in 2 minutes. The dosage varies from 150 to 250 mg. depending upon the patient's reaction. Very often this will be sufficient to carry the patient through delivery with good amnesia with the use of pudendal block or local infiltration for the episiotomy site. However, in cases of slow labor, a second, usually smaller, injection of pentobarbital will be necessary. If it is given shortly before delivery, repair of the episiotomy is possible without a local anesthetic.

All the physicians on the staff now use pentobarbital anesthesia with minor differences in method. Variations are mainly found in the use of tranquilizers and in the timing of the pentobarbital injection. A few physicians give pentobarbital earlier than I do, while others give pentobarbital late in the second stage of labor.

In breech presentation, local infiltration of mepivacaine (Carbocaine) is used for the episiotomy, and pentobarbital is first given when the infant is delivered to the level of the umbilicus. At this time 3 to 5 c.c. of pentobarbital is given rather rapidly, and the in-

fant is delivered by partial breech extraction.

The level of anesthesia is usually satisfactory for common surgical procedures in obstetrics, such as low forceps delivery, forceps rotation, breech delivery, and version and extraction of a second twin.

When pentobarbital was first used in our department, it was often supplemented with ether for the delivery; however, as we gained experience, we found that the babies actually did much better when a larger amount of pentobarbital was given rather than when ether was given. Little by little, ether has, therefore, been virtually eliminated from our service. In my last 1,000 cases, ether anesthesia was used one time only for version and extraction of a second twin. This experience has been nicely confirmed by Phillips.[8]

Contraindications. Contraindications to pentobarbital are conditions with impaired liver function and conditions with depressed or obstructed respiration. We have found, as have others,[9] that pentobarbital can be given safely to patients with toxemia. Naturally, pentobarbital should not be administered to patients who are known to be sensitized to barbiturates.

All patients admitted with bleeding are very carefully screened and usually should not receive pentobarbital because of danger of shock and since the health and security of the mother and baby are possibly already jeopardized.

Severe prematurity is a contraindication because of the premature infant's lessened resistance to all analgesia and anesthesia.

Table III. General statistics regarding deliveries

1,000 patients	1,005 infants
378 primipara	622 multipara
807 spontaneous deliveries	145 low forceps
49 breech deliveries	3 version and extraction
1 cesarean section	785 episiotomies

Table IV. Dosage of pentobarbital given to patients

1,000 patients	305 mg.
378 primipara	338 mg.
622 multipara	284 mg.
488 patients	250 mg.
Maximum	650 mg.
Minimum	100 mg.

Material

I have delivered slightly more than 2,000 patients under pentobarbital anesthesia. The results of the last 1,000 pentobarbital anesthesia administrations given to my private white patients are shown in Tables III and IV.

Effect of pentobarbital on the mother

Maternal safety and results may be determined by evaluation of the following factors:

1. Blood pressure is usually not influenced by pentobarbital when given in moderate doses.

2. Respiration. Patients who are nervous and hyperventilating will often have a short period of apnea following the initial injection. However, respiration is always restored spontaneously in a couple of minutes, probably when the abnormally low CO_2 tension returns to normal.

Laryngeal spasm is a theoretical hazard of intravenous injection of the ultrashort-acting barbiturates; however, I have never seen it following an injection of pentobarbital, and it has, as far as I have been able to ascertain, never taken place in any of our 11,820 patients.

3. Local reaction. Pentobarbital sodium is a very alkaline solution and causes pain, tenderness, and infiltration when given subcutaneously; therefore, caution should be exercised during injection. Occasionally, a very mild, self-limiting, superficial phlebitis is seen in the cubital vein which is usually the preferred site of injection. I have, however, never seen any sloughing or any patient actually being incapacitated because of erroneous perivenous injection.

4. Amnesia is usually good from the moment pentobarbital is given, and I have, therefore, used scopolamine only very occasionally, nearly exclusively, in cases of pri-

mary uterine inertia before meperidine and pentobarbital were given.

5. Hyperactivity. When pentobarbital is given following premedication with meperidine and propiomazine, hyperactivity is fairly rare. The patients will be resting quietly between contractions with some groaning and moderately increased restlessness with the contractions. In 14 cases out of 1,000 it was noted in the chart that the patient was difficult to restrain.

6. Vomiting. All my maternity patients are instructed not to eat from the moment they are in labor. However, it cannot be avoided that some patients are admitted a few hours following a meal. Naturally, no general anesthetic causing anesthesia of this level should be given to a patient who has eaten recently. However, whether or not anesthesia is safe must be decided in each case depending upon the type and amount of food ingested. Pentobarbital, 250 mg., given intravenously, very slowly, will hardly be enough to suppress the coughing reflex if it is more than 2 hours since the patient was given meperidine and propiomazine, and the patient will be able to cough and, therefore, not aspirate.

In spite of close attention to this point, 3 of my patients vomited small to moderate amounts, while one vomited profusely. None had signs of aspiration, and all had an afebrile postpartum course.

This paper was from its beginning aimed at showing what can be accomplished with pentobarbital anesthesia as given by the attending nurse and obstetric staff; however, to get the full picture, it is here necessary to mention that one patient, admitted to our department by another physician, was given 250 mg. of pentobarbital by an anesthesiologist and vomited profusely, aspirated, was asphyxiated, and died from cardiac arrest.

7. Uterine contractions are not much influenced by pentobarbital. The total number of patients where it was felt that labor slowed down following pentobarbital was only 20 or 2 per cent. Conversely, it was felt that in many cases labor was shortened because the patient could not hold back following administration of pentobarbital. The patients are able to bear down well in the second stage as witnessed by the fact that only 145 patients were delivered by forceps while 807 delivered spontaneously (Table III).

8. Postpartum bleeding secondary to uterine relaxation is rare. All my patients are routinely given methylergonovine maleate (Methergine) 0.2 mg. I.V. following delivery. In only 19 patients, 1.9 per cent, was it found necessary to give additional medication. This low incidence also witnesses to the fact that the uterine contractions are not inhibited.

9. Recovery. Pentobarbital is a short-acting, but not ultrashort-acting barbiturate. It is metabolized fairly rapidly, and the patient will usually be awake in one to four hours after injection of our average dose. Naturally, it is necessary to observe them in the labor rooms during this time.

Effect of pentobarbital on the newborn

While it may be fairly easy to evaluate the effect of a drug on the parturients, it is very difficult to objectively evaluate the relation between the drugs given to the mother and the condition of the newborn because the numerous variable factors of pregnancy, labor, and delivery may affect the newborn. The following factors must be evaluated:

1. Stillbirth. In order for a drug to be safe, it must not be the cause of stillbirth. Of 1,005 infants, 9 were stillborn. Six fetuses died before labor and were born macerated. In one case, no fetal heart sound was heard on admission at 30 weeks' gestation following complete abruptio of the placenta. One fetus died during labor from congenital malformation before pentobarbital was given. One fetus, weighing 1 pound, 5 ounces, died during labor after the mother received 250 mg. of pentobarbital (Table V).

2. Neonatal death. Our drugs of choice

Table V. Stillbirth

Macerated fetuses	6
Died before injection of pentobarbital	2
Died following injection of pentobarbital, 1 pound, 5 ounces	1

Table VI. Causes of neonatal death

Anencephalic	1
Hydrocephalic	1
Congenital heart anomalies	1
Extreme immaturity	2
Multiple congenital anomalies of alimentary tract	1
Congenital defects in fat metabolism, died at 3 months old	1

Table VII. Possible connection between resuscitation and obstetric complications

Postmaturity	3
Prematurity	4
FHS irregular before pentobarbital	2
Placental dysfunction	6
Toxemia	4
Cord 3 times tight around neck	3
Prolonged second stage	9

Table VIII. Apgar score of 100 consecutive newborn infants

Apgar score	*Newborn infants*	*Infants resuscitated*
10	0	0
9	41	0
8	35	0
7	17	2
6	6	5
1	1	0

Table IX. Neonatal morbidity

	No.
Congenital heart anomalies	6
Sleepy in nursery	3
Hyaline membrane disease, 33 and 36 weeks	2
Episodes of cyanosis in nursery	3
Irritable, ruddy complexion	1
Grunty respiration, 38 weeks	1
Scattered atelectases, 37 weeks	1
Spastic paraplegia	1
Total	18

must not be the cause of neonatal death. Of 1,005 infants, 7 died neonatally, all from causes beyond our control (Table VI).

3. Resuscitation. The ease and speed with which the infants establish extrauterine respiration, circulation, and oxygenation is a good measure of their condition. All newborn infants are immediately aspirated with bulb syringe. If their color is not satisfactory within one or 2 minutes, in my or the attending nurse's opinion, an oxygen mask is held in front of their face. If they do not immediately respond to this, they will be resuscitated using intermittent positive pressure. Seventy-four babies received oxygen by mask for varying degrees of sluggishness and cyanosis, while 14 infants were resuscitated using intermittent positive pressure. This means that 8.8 per cent of the infants received oxygen in the delivery room; however, obstetric complications were found in 31 of these labor cases (Table VII).

Of the 88 infants resuscitated, 87 showed no evidence of permanent damage which could be related to labor, delivery, or anesthesia. However, one infant lived with evidence of permanent brain damage.

4. The Apgar score[1] has been generally accepted as an objective way of evaluating a newborn baby's condition. In a partially separate study, 100 consecutive babies were evaluated (Table VIII).

Since only a very few newborn babies' hands are pink at one minute, I have not given any infant a 10 score. The only infant with a score lower than 6 was a 22 week, 1 pound newborn infant who had only a faint heartbeat and died in 55 minutes.

5. Neonatal morbidity is an important indicator in evaluating trauma of pregnancy, delivery, analgesics, and anesthesia. Eighteen infants had neonatal complications which they survived. Six had congenital malformations of the heart. Eleven had minor complications, but all recovered completely and were discharged with the mother (Table IX).

One infant did poorly from birth, needed resuscitation in the delivery room, and remained limp with episodes of cyanosis. It was transferred to a university pediatric department and was discharged with a diagnosis of spastic paraplegia, cause undetermined. This patient had bleeding early in pregnancy and at two occasions took a large amount of an undetermined drug. In labor she was

given no analgesia and a total of 500 mg. of pentobarbital divided into three doses and spontaneous delivery took place following a slightly prolonged second stage.

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Discussion

Dr. Hugh A. McAllister, Lumberton, North Carolina. It is somewhat encouraging to know that the search for a safe, sound, and satisfactory anesthesia for the parturient female continues. In general, the smaller the hospital, the less chance there is of satisfactory anesthesia in delivery rooms.

Dr. Scear shows in Table II the number of patients receiving meperidine and various tranquilizers and in various doses but does not tell us his criteria for when to give the medication, the necessity for repeating it, and how he decides on the need and the dose for the second administration. The same is true of his administration of pentobarbital. How early in labor should it be given? Should the condition of the cervix and the vigor of labor be deciding factors?

Since our experience has been totally with sodium pentothal which is an ultrashort-acting barbiturate and since it is the sulfur analogue of pentobarbital sodium, I should like to briefly show our experience with that drug, and I feel that our experience with sodium pentothal and his with pentobarbital sodium should not differ greatly.

In 1955, Dr. Charles E. Flowers, Jr., and I reported on the use of sodium pentothal in 7,793 deliveries between the years of 1948 and 1955 showing that for the last 5 years of that period 82 per cent of the deliveries at Southeastern General Hospital were done under sodium pentothal. Since then, an additional 23,723 deliveries have been done with approximately 95 per cent being done under sodium pentothal. It is my feeling that 35,311 deliveries with approximately 90 per cent being done under thiopental signifies the acceptance of the obstetric staff and the patients in our community.

This critical analysis of our work should also fully apply to Dr. Scear's work with pentobarbital.

Pentothal sodium is a thiobarbiturate which is primarily a parasympathomimetic hypnotic but when used in conjunction with nitrous oxide, oxygen, cyclopropane, ether, and conduction anesthesia, it becomes a useful agent in the practice of anesthesia. Being a parasympathomimetic, laryngospasm could be easily produced by perineal stretching at the time of delivery. Being primarily a hypnotic, it would seem that profound cerebral depression would be necessary to alleviate the pain of a parturition. Being a potent hypnotic, fetal depression could be an undesirable complication. Apparently, however, thiopental is a useful agent in obstetrics.

When pentothal sodium is used intermittently and intelligently in patients who have not ingested a recent meal and have had parasympathetic depression by scopolamine, atropine, or the like, laryngospasm is not a significant complication. There were no maternal deaths due to anesthesia and no serious laryngospasms in this series. Conservative doses of 5 per cent pentothal give sufficient cerebral depression to alleviate pain but apparently not sufficient to depress the more primitive medullary centers. Solutions of 2.5 per cent are less satisfactory and are not recommended for thiopental hypnosis for delivery.

The lack of fetal depression is more difficult to explain. The rapid passage of thiobarbiturates across the placenta is a fact. The rapid disappearance of thiopental from the bloodstream and its concentration in body fat is likewise well established.

There is no real correlation between infant blood level of pentothal and the reaction time of the infant. Intermittent injection of pentothal, the rapid dispersal of pentothal in the tissue spaces and fat and the unpredictable placental circulation at time of delivery can account for these variations. It is factual, though not easily understandable, that despite almost equal blood concentrations of pentothal in the mother and the fetus, a vigorous crying infant can be delivered of a mother who is asleep. To explain this one must think hypothetically. Thiobarbiturates rapidly leave the bloodstream and enter tissue spaces.

If only a small amount of pentothal is used, time is not a factor in fetal depression, since the pentothal will leave both maternal and infant circulation rapidly. However, if large intermittent doses are employed over prolonged periods of time, tissue saturation may occur and pentothal can then be responsible for depression in the infant. In this series small doses were used for short times.

A second factor may be the presence of drug tolerance and adaptability of a newborn infant. Possibly, the primitive urge to establish extrauterine respiration is profound. The fact that only 5 per cent of the infants required resuscitation may be a sampling error. However, this low figure may also be indicative of the safety of the technic. Moreover, in the entire series of the first 7,793 deliveries, there were no infant deaths that were attributable to anesthesia per se. The last 23,723 deliveries have not been completely analyzed. It is evident that the majority of the patients received less than 300 mg. of pentothal and were anesthetized less than 5 minutes prior to delivery.

It seems to me that prerequisites for any type anesthesia, in general, and pentothal or pentobarbital, in particular, should be:

1. The patient should not have ingested solid food less than 2 hours before onset of labor.

2. Oxygen should be administered with pentothal sodium (or pentobarbital) since the arterial oxygen saturation may fall during its administration.

3. Persons who are responsible for pentothal (or pentobarbital) anesthesia should have both the materials necessary and the technical knowledge to treat laryngospasm.

4. The administration of pentothal sodium should be delayed until the total amount of pentothal which is given prior to delivery should not exceed 0.5 Gm.

Our method of administration of pentothal is as follows: 1 Gm. of pentothal is mixed with 20 c.c. of distilled water to make a 5 per cent solution. The resulting solution contains 50 mg. per cubic millimeter.

The initial dose should not exceed 200 mg. in the first 30 to 60 seconds. Anesthesia is maintained with intermittent doses of 50 mg. No attempt is made to predetermine the total dose required. There is wide variation in the individual tolerance to thiobarbiturates. All drugs should be given by vein and not intramuscularly.

Pentothal anesthesia in obstetrics should be used in combination with a pudendal block, paracervical block, or at least local perineal infiltration for maximum efficiency. Although in our series many operative procedures were attempted it is not our feeling that forceps rotation, delivery of a complicated breech, version and extraction of a second twin, or other real obstetric problems should be attempted under pentothal alone because adequate relaxation is not possible.

That barbiturates do have a place in obstetric delivery is in my mind a certainty but just what place remains somewhat of a question. Certainly pentothal is safer, far more esthetic than most inhalation types of anesthesia with obstructed breathing, slow ioduction, and postdelivery nausea, and we will certainly welcome continued observation of this useful drug to more completely establish its value in our chosen field.

DR. JOHN C. BURWELL, Greensboro, North Carolina. Dr. Seear has presented further evidence of the efficacy and safety of intravenous barbiturates for labor and delivery. He has used other synergistic drugs to obtain analgesia as well as anesthesia. The results, compiled over a period of years, bear out the findings of other investigators and substantiate contentions regarding length of labor, bleeding, fetal depression, morbidity, and mortality.

In our own experience, we have found that intravenous barbiturates provide an adequate margin of safety with a satisfactory degree of anesthesia. We have not used the intravenous administration for analgesia. We are in complete accord with the author's statement that "Ideally

all obstetric anesthesia should be administered by an anesthesiologist trained in obstetric anesthesia." At the same time, the intravenous barbiturates do provide maternal pain relief where more sophisticated coverage is unavailable, and the author's careful and comprehensive studies are a definite contribution to our knowledge of the subject.

DR. SEEAR (Closing). To Dr. McAllister's question, I can say that I do not adhere strictly to a routine but give meperidine and propiomazine when labor is well established, as proved by progressive effacement and dilatation of the cervix and regular, painful contractions, usually when the cervix is from 2 to 4 cm. dilated.

Pentobarbital is given when the patient again becomes complaining, usually when the cervix is from 5 to 8 cm. dilated, and additional pentobarbital is given if the patient becomes alert before she is ready for delivery.

EXHIBIT 6

PHARMACOLOGY AND THE NURSING PROCESS

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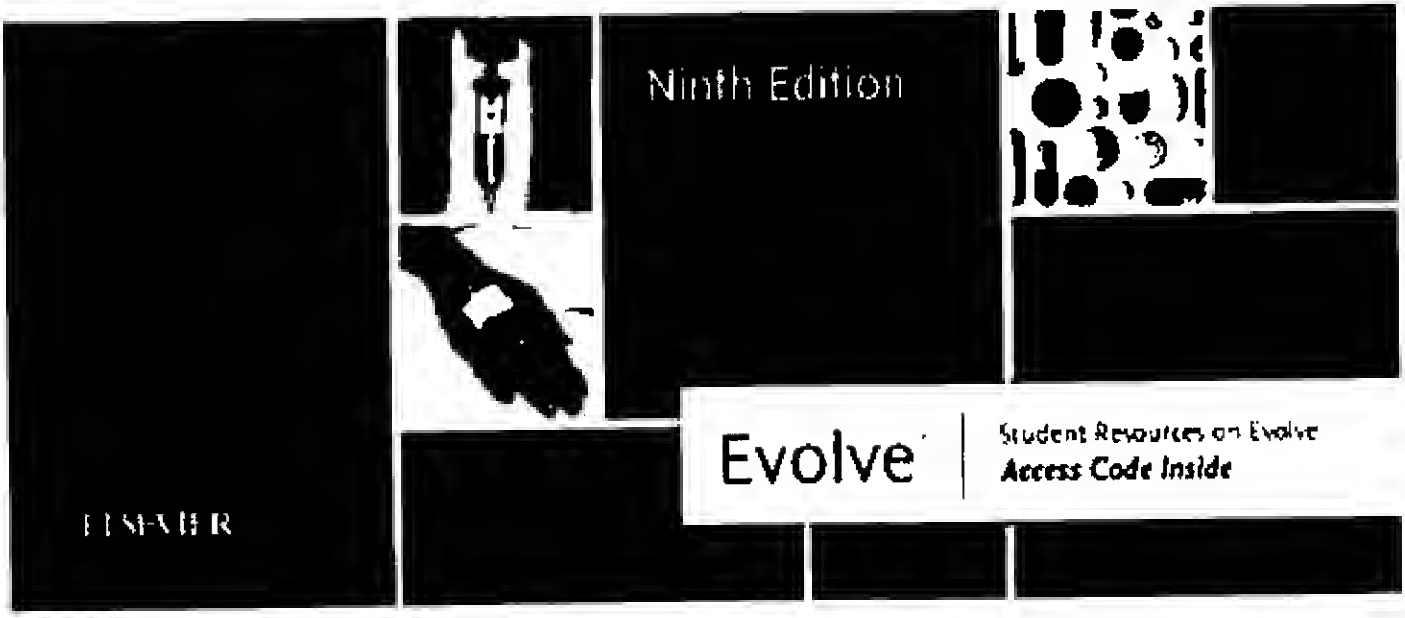
Rainforth Collins
Snyder



PHARMACOLOGY AND THE NURSING PROCESS Ninth Edition

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TABLE 12.5 Sedative-Hypnotic Barbiturates

Generic Name	Trade Name
Ultrashort Acting	
methohexital	Brevital
thiopental	Pentothal
Short Acting	
pentobarbital	Nembutal
secobarbital	Seconal
Intermediate Acting	
butabarbital	Butisol
Long Acting	
phenobarbital	Generic
mephobarbital	Mebaral

cerebral cortex. Their ability to inhibit nerve impulse transmission is due in part to their ability to potentiate the action of the inhibitory neurotransmitter GABA, which is found in high concentrations in the CNS. Barbiturates also raise the seizure threshold and can be used to treat seizures (see Chapter 14).

Indications

All barbiturates have the same sedative-hypnotic effects but differ in their potency, time to onset of action, and duration of action. It is important to note that the use of barbiturates is no longer recommended for sleep induction. The various categories of barbiturates can be used for the following therapeutic purposes: (1) ultrashort acting: anesthesia for short surgical procedures, anesthesia induction, control of convulsions, and reduction of intracranial pressure in neurosurgical patients; (2) short acting: sedation and control of convulsive conditions; (3) intermediate acting: sedation and control of convulsive conditions; and (4) long acting: epileptic seizure prophylaxis.

Contraindications

Contraindications to barbiturate use include known drug allergy, pregnancy, significant respiratory difficulties, and severe kidney or liver disease. These drugs must be used with caution in older adults due to their sedative properties and increased fall risk.

Adverse Effects

Adverse effects of barbiturates relate to the CNS and include drowsiness, lethargy, dizziness, hangover, and paradoxical restlessness or excitement. Their long-term effects on normal sleep architecture can be detrimental. Barbiturates deprive people of REM sleep, which can result in agitation. When any barbiturate is stopped, a rebound phenomenon may occur. During this rebound, the proportion of REM sleep is increased and nightmares often ensue. Common adverse effects of barbiturates are listed in Table 12.6. As is the case with most sedative drugs, barbiturates are associated with an increased incidence of falls when used in older adults. If they are recommended for older adults at all, the usual dose is reduced by half whenever possible.

TABLE 12.6 Barbiturates: Adverse Effects

Body System	Adverse Effects
Cardiovascular	Vasodilation and hypotension, especially if given too rapidly
Gastrointestinal	Nausea, vomiting, diarrhea, constipation
Hematologic	Agranulocytosis, thrombocytopenia
Nervous	Drowsiness, lethargy, vertigo
Respiratory	Respiratory depression, cough
Other	Hypersensitivity reactions: urticaria, angioedema, rash, fever, Stevens-Johnson syndrome

Toxicity and Management of Overdose

Treatment of an overdose is mainly symptomatic and supportive. The mainstays of therapy are maintenance of an adequate airway, assisted ventilation, and oxygen administration if needed, along with fluid and pressor support as indicated. Activated charcoal may be given; however, recent clinical data do not support its use because no improvement in clinical outcome has been shown. Phenobarbital and mephobarbital are relatively acidic and can be eliminated more quickly by the kidneys when the urine is alkalized (pH is raised). This keeps the drug in the urine and prevents it from being resorbed back into the circulation. Alkalization, along with forced diuresis using diuretics (e.g., furosemide [see Chapter 28]), can hasten elimination of the barbiturate.

Interactions

Barbiturates as a class are notorious enzyme inducers. They stimulate the action of enzymes in the liver that are responsible for the metabolism or breakdown of many drugs. By stimulating the action of these enzymes, they cause many drugs to be metabolized more quickly, which usually shortens their duration of action. Barbiturates increase the activity of hepatic microsomal or cytochrome P-450 enzymes (see Chapter 2). This process is called *enzyme induction*. Induction of this enzyme system results in increased drug metabolism and breakdown. However, if two drugs are competing for the same enzyme system, the result can be inhibited drug metabolism and possibly increased toxicity for the wide variety of drugs that are metabolized by these enzymes. Other drugs that are enzyme inducers are rifampin and phenytoin.

Additive CNS depression occurs with the coadministration of barbiturates with alcohol, antihistamines, benzodiazepines, opioids, and tranquilizers. Drugs most likely to have marked interactions with the barbiturates include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (see Chapter 16), anticoagulants (see Chapter 26), glucocorticoids (see Chapter 30), and oral contraceptives (see Chapter 34) with barbiturates. Coadministration of MAOIs and barbiturates can result in prolonged barbiturate effects. Coadministration of anticoagulants with barbiturates can result in decreased anticoagulation response and possible clot formation. Coadministration of barbiturates with oral contraceptives can result in accelerated metabolism of the contraceptive drug and possible unintended pregnancy. Women taking both types of medication concurrently need to

TABLE 12.7 Barbiturates: Controlled Substance Schedule

Schedule	Barbiturates
C-II	pentobarbital, secobarbital
C-III	butalbital, vinbarbital
C-IV	mephobarbital, methohexital, phenobarbital

be advised to consider an additional method of contraception as a backup.

Dosages

Barbiturates can act as either sedatives or hypnotics, depending on the dosage. For information on selected barbiturates and their recommended sedative and hypnotic dosages, see the following table.

Dosages

Selected Barbiturates

Drug	Onset and Duration	Usual Dosage Adult: Range	Indications/ Uses
pentobarbital (Nembutal)	Short acting	IM: 150–200 mg IV: 100 mg	Preoperative sedative
phenobarbital	Long acting	PO: 30–120 mg/day divided IM/IV: 100–200 mg 60–90 min before surgery	Sedative Preoperative sedative

DRUG PROFILES

Like benzodiazepines, barbiturates can also have varied uses, including preoperative sedation, anesthesia adjunct, and anticonvulsant therapy. All barbiturates are controlled substances, but not all are on the same schedule, as illustrated in Table 12.7. Dosage information appears in the dosages table for barbiturates.

pentobarbital

Pentobarbital (Nembutal) is a short-acting barbiturate. Formerly prescribed as a sedative-hypnotic for insomnia, pentobarbital is now principally used preoperatively to relieve anxiety and provide sedation. In addition, it is used occasionally to control status epilepticus. Pentobarbital may also be used to treat withdrawal symptoms in patients who are physically dependent on barbiturates or nonbarbiturate hypnotics. It is available in oral, injectable, and rectal dosage forms.

Pharmacokinetics: Pentobarbital

Route	Onset of Action	Peak plasma Concentration	Elimination Half-Life	Duration of Action
PO	30–60 min	1–2 hr	20–45 min	3–4 hr

phenobarbital

Phenobarbital is considered the prototypical barbiturate and is classified as a long-acting drug. Phenobarbital is used for the prevention of generalized tonic-clonic seizures and fever-induced convulsions. In addition, it has been useful in the treatment of hyperbilirubinemia in neonates. Currently it is only rarely used as a sedative and is no longer recommended to be used as a hypnotic drug. It is available in oral and injectable forms.

Pharmacokinetics: Phenobarbital

Route	Onset of Action	Peak Plasma Concentration	Elimination Half-Life	Duration of Action
IV	5 min	30 min	50–120 hr	8–12 hr
PO	30 min	1–6 hr	50–120 hr	8–12 hr

OVER-THE-COUNTER HYPNOTICS

Nonprescription sleeping aids often contain antihistamines (see Chapter 36). These drugs have a CNS depressant effect. The most common antihistamines contained in over-the-counter sleeping aids are doxylamine (Unisom) and diphenhydramine (Sominex). Analgesics (e.g., acetaminophen [see Chapter 10]) are sometimes added to offer some pain relief if pain is a component of the sleep disturbance (e.g., acetaminophen/diphenhydramine [Extra Strength Tylenol PM]). As with other CNS depressants, concurrent use of alcohol can cause additive CNS depression.

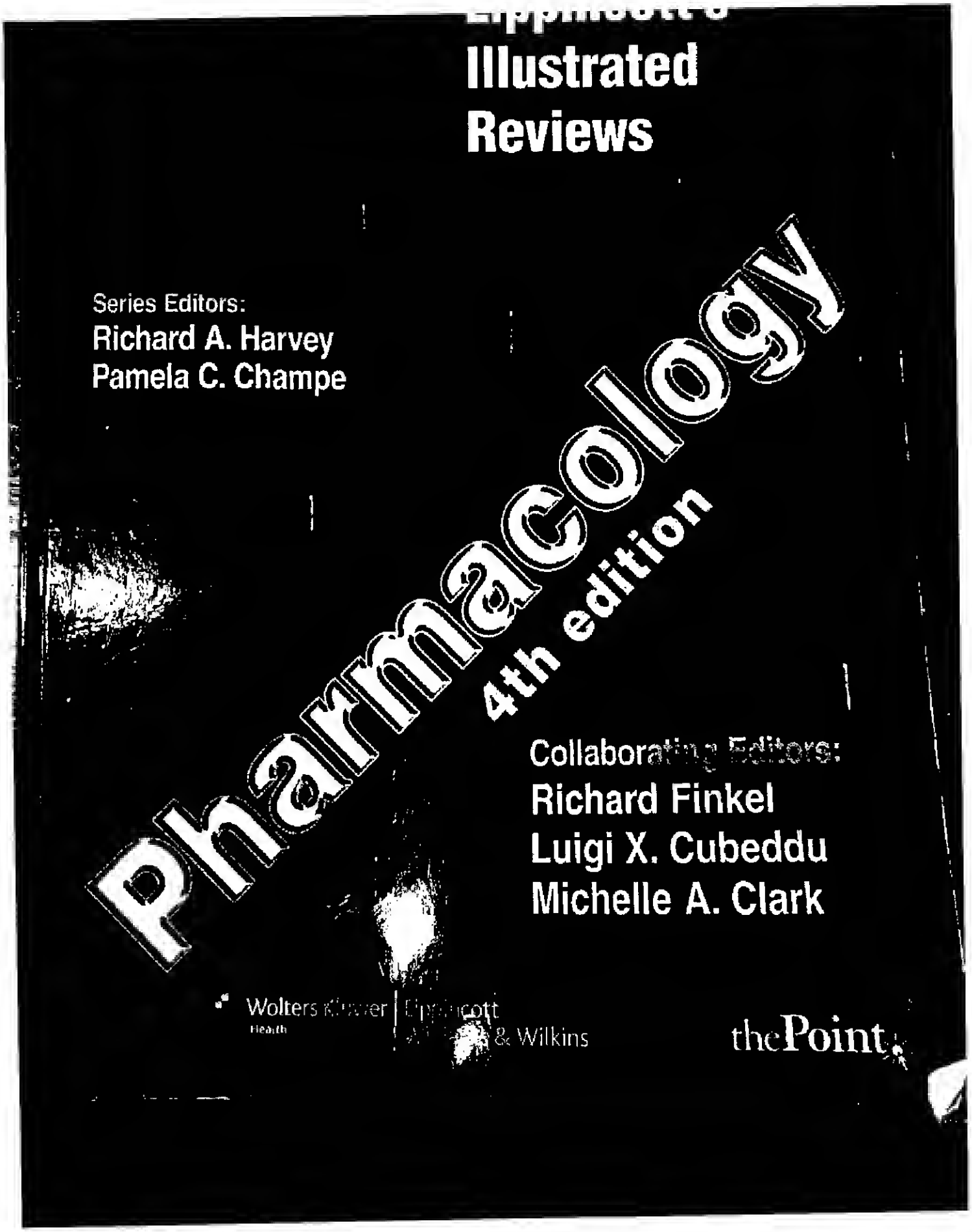
MUSCLE RELAXANTS

A variety of conditions such as trauma, inflammation, anxiety, and pain can be associated with acute muscle spasms. The muscle relaxants are a group of compounds that act predominantly within the CNS to relieve pain associated with skeletal muscle spasms. Most muscle relaxants are known as *centrally acting* skeletal muscle relaxants because their site of action is the CNS. Centrally acting skeletal muscle relaxants are similar in structure and action to other CNS depressants such as diazepam. It is believed that the muscle relaxant effects are related to this CNS depressant activity. Only one of these compounds, dantrolene, acts directly on skeletal muscle. It belongs to a group of relaxants known as direct-acting skeletal muscle relaxants. It closely resembles GABA.

Mechanism of Action and Drug Effects

The majority of the muscle relaxants work within the CNS. Their beneficial effects are believed to come from their sedative effects rather than from direct muscle relaxation. Dantrolene acts directly on the excitation-contraction coupling of muscle fibers and not at the level of the CNS. It directly affects skeletal muscles by decreasing the response of the muscle to stimuli. It appears to exert its action by decreasing the amount of calcium released from storage sites in the sarcoplasmic reticula of muscle fibers. All other muscle relaxants have no direct effects on muscles, nerve conduction, or muscle-nerve junctions and have a depressant effect on the CNS. Their effects are the result of CNS depression in the brain primarily at the level of the brainstem, thalamus, and basal ganglia and also at the spinal cord. The effects of muscle relaxants are relaxation of striated muscles,

EXHIBIT 7



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The barbiturates were formerly the most widely used drugs to sedate the patient or to induce and maintain sleep. However, they have largely been replaced by the benzodiazepines, primarily because of their high potential for tolerance, drug-metabolizing enzymes, physical dependence, and the fact that withdrawal is associated with very severe withdrawal symptoms. Foremost is their ability to cause coma in toxic doses. Certain barbiturates, such as the very short-acting *thiopental*, are still used to induce anesthesia (see p. 135).

A. Mechanism of action

The sedative-hypnotic action of the barbiturates is due to their interaction with $GABA_A$ receptors, which enhances GABAergic transmission. The binding site is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride channel openings. In addition, barbiturates can block excitatory glutamate receptors. Anesthetic concentrations of *pentobarbital* also block high-frequency sodium channels. All of these molecular actions lead to decreased neuronal activity.

B. Actions

Barbiturates are classified according to their duration of action (Figure 9.7). For example, *thiopental* [thye-oh-PEN-tal], which acts within seconds and has a duration of action of about 30 minutes, is used in the intravenous induction of anesthesia. By contrast, *phenobarbital* [fee-noe-BAR-bi-tal], which has a duration of action greater than a day, is useful in the treatment of seizures (see p. 178). *Pentobarbital* [pen-toe-BAR-bi-tal], *secobarbital* [see-koe-BAR-bi-tal], and *amobarbital* [am-oh-BAR-bi-tal] are short-acting barbiturates, which are effective as sedative and hypnotic (but not antianxiety) agents.

1. **Depression of CNS:** At low doses, the barbiturates produce sedation (calming effect, reducing excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose. Barbiturates do not raise the pain threshold and have no analgesic properties. They may even exacerbate pain. Chronic use leads to tolerance.

Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to CO_2, and overdose is followed by respiratory depression and death.

Liver enzyme induction: Barbiturates induce P450 and normal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are dependent on metabolism to maintain their concentration.

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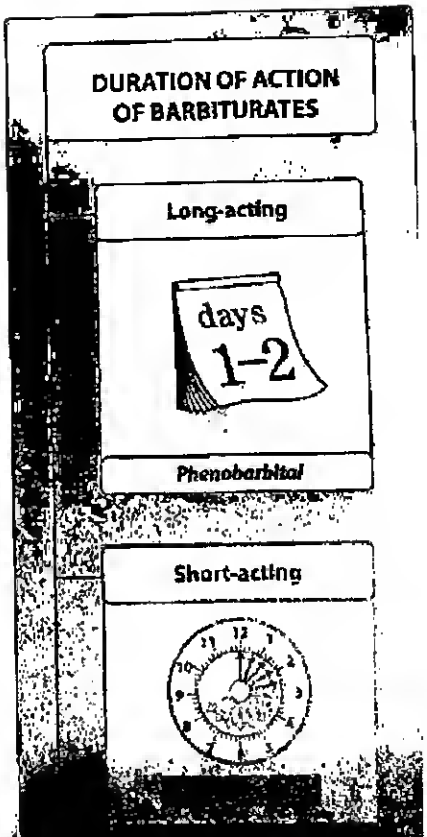

EXHIBIT 8

PEDIATRIC EMERGENCY PROCEDURES

Christopher King
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is more effective when administered to a child with an empty stomach. Absorption may be erratic in those who have recently eaten, leading to an unpredictable onset of action and depth of sedation. The usual dose is 0.2 to 0.6 mg/kg, and the maximum clinical effect may not occur for 25 to 40 minutes.

The major complications of benzodiazepines are respiratory depression, which is almost exclusively associated with intravenous administration although it occasionally is reported with intramuscular injections. Complications are minimal when benzodiazepines are used as a single agent or when they are administered by the oral or nasal route. However, because benzodiazepines act synergistically with narcotics and barbiturates, their effects—and potential complications—are increased when they are used in conjunction with these other agents. In addition, some children who receive benzodiazepines experience a so-called "paradoxical" reaction. Rather than being sedated, these patients become more anxious and agitated after administration of the medication. In such cases, it appears that the child predominantly experiences the disinhibitory effect of the drug instead of the sedative effect. Although paradoxical reactions can be unnerving, usually they may also respond favorably to administration of additional benzodiazepine.

Flumazenil is a benzodiazepine antagonist that blocks the activity of benzodiazepines at CNS receptor sites. Its use in the pediatric population has not been widely studied. It may be appropriate in cases of excessive sedation or when adverse side effects are experienced but is not recommended for routine use to reduce the duration of benzodiazepine-induced sedation. The pediatric dose of flumazenil is 0.01 mg/kg, given by slow intravenous infusion, up to a maximum of 1 mg. The onset of action is within 1 to 3 minutes. Patients must be monitored closely for sedation because the effects of flumazenil subside before the sedative effects of the benzodiazepine. Additionally, flumazenil exhibits some potential toxicities and effects. Most are minor and include crying, agitation, headache, and dizziness. However, it has rarely been associated with seizures.

Barbiturates

Barbiturates are sedative-hypnotics that act as general depressants of the central and peripheral nervous systems and of skeletal, smooth, and cardiac muscles. Their clinical effects are dose dependent and may widely from mild sedation to coma. Barbiturates can be divided into four groups: ultrashort-acting (thiopental and methohexital), short-acting (pentobarbital), intermediate (butalbarbital), and long-acting (phenobarbital). Generally, the ultrashort-acting and short-acting barbiturates are selected for procedural sedation. When used alone at the proper sedative dose, adverse side effects are rare. Higher doses, e.g., a premedication dose of methohexital, can, however, cause apnea, transient hypotension, and bradycardia. Barbiturates have no analgesic qualities when used at sedative doses; analgesia is only provided when high anesthetic doses are administered. Thus, when the patient is anticipated to experience pain, an additional analgesic (parenteral or local) must be used.

Methohexital Methohexital is an ultrashort-acting barbiturate that may be given rectally for brief, painless procedures or procedures with which local anesthetic will be used. The onset of action is approximately 5 minutes. When used as a sedative for painless procedures (e.g., CT scan, MRI), it is 95% effective. IV: The methohexital dose is 1.5 mg/kg per bolus, up to a maximum dose of 2 g. Adverse events include hypoventilation and oxygen desaturation, hiccups, cough, and hyperexcitation. Although methohexital can also be given by intravenous injection, there are few data regarding this route of administration for pediatric procedural sedation. Furthermore, safer alternative agents are available.

Pentobarbital Pentobarbital is a short-acting barbiturate that is useful for longer procedures or as a preoperative sedative. It can be used in conjunction with an analgesic for painful procedures and may be given parenterally, orally, or rectally. When administered as an intravenous injection, onset of action for pentobarbital occurs in approximately 3 minutes, and the duration of effect is approximately 60 minutes. Oral administration and rectal administration are associated with a delayed onset of sedation, up to 45 minutes. Successful sedation occurs in approximately 90% of patients, but the best sedation results are seen in children younger than 6 years of age [13,37]. The oral, rectal, or intramuscular dose of pentobarbital is 2 to 6 mg/kg, up to a maximum dose of 150 mg. The intravenous dose of pentobarbital is 1 to 3 mg/kg. Adverse events associated with pentobarbital administration include respiratory depression, emergence reactions, and paradoxical hyperactivity.

Chloral Hydrate

Chloral hydrate is a sedative-hypnotic CNS depressant used in children as a sedative for procedures which are painless but require cooperation, such as CT scan, MRI, or electroencephalogram (EEG). It can also be used in conjunction with a local anesthetic for mildly painful procedures such as minor dental work or wound repair [31,38]. The drug is readily absorbed through the gastrointestinal tract and may be administered orally or rectally. The dose is 25 to 100 mg/kg, up to a maximum of 1 g in children and 2 g in children. Peak therapeutic levels occur in approximately 30 to 60 minutes. Chloral hydrate is metabolized in the liver to its active metabolite, trichloroethanol. The elimination half-life of this metabolite is 8 to 12 hours.

When chloral hydrate is administered at low doses (e.g., 25 mg/kg) for light sedation, monitoring beyond the initial period of sedation need only consist of periodic assessment of vital signs. Patients given higher doses of the drug (50 to 100 mg/kg) should be monitored with continuous pulse oximetry. Adverse side effects include excessive somnolence and paradoxical excitation. Major disadvantages of chloral hydrate use include lack of a reversal agent, unpredictable onset and degree of sedation, and a long half-life that requires a prolonged period of monitoring.

EXHIBIT 9

TIETZ *Textbook of*
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is not formed from α-hydroxyamines. However, the requirement for amphetamine ≥200 ng/mL may not be satisfied in some cases of known methamphetamine ingestion, especially during the initial 12 hours postdose period, leading to false-negative results.[457,490] To increase detection rate for amphetamine and methamphetamine, SAMHSA has proposed[432] a reduction of the screening and confirmation cutoff from 1000 ng/mL and 500 ng/mL to 500 ng/mL and 250 ng/mL, respectively. Methamphetamine would require the presence of at least 100 ng/mL amphetamine metabolite for a positive result. In a 2002 study,[345] these lower cutoff values increased the detection rate for methamphetamine by 48% compared with current cutoff values. Moreover, the highest detection rate for methamphetamine was achieved by use of the 250 ng/mL cutoff with elimination of the amphetamine requirement. In the described procedure, periodate oxidation before derivatization destroys α-hydroxyamines and therefore eliminates possible false report of methamphetamine owing to their presence.[147]

Barbiturates

The barbiturates have a low therapeutic index and a relatively high abuse potential. Because of their rapid onset and short duration of action, the short- to intermediate-acting barbiturates are used as sedative-hypnotics (amobarbital, butabarbital, butalbital, pentobarbital, and secobarbital) and are those most commonly abused. The longer acting barbiturates (mephobarbital and phenobarbital), used primarily for their anticonvulsant properties, are rarely abused.

Pharmacological Response

Barbiturates suppress CNS neuronal activity and thus have sedative and hypnotic properties.[186] This CNS suppression is a result of barbiturate-enhanced activation of the inhibitory GABA-ergic neuronal system mediated by the neurotransmitter γ-aminobutyric acid (GABA).[86] Postsynatic $GABA_A$ receptors are multisubunit transmembrane Cl^- conductance channels, which when activated by GABA open to allow flow of Cl^- into the neuron, with subsequent hyperpolarization and inhibition of electrical transmission. At low dose, some barbiturates bind to the $GABA_A$ receptors and enhance their response to GABA. At a higher dose, barbiturate binding results in prolonged opening of the Cl^- channel, without the necessity for GABA binding. In addition, barbiturates suppress excitatory glutamate-responsive AMPA (alpha-amino-3-OH-4-isoxozole propionic acid) ion-gated receptor subtypes.

Because of their low therapeutic index and high potential for abuse, the barbiturates have largely been replaced by the safer benzodiazepines for sedative and hypnotic purposes. Nevertheless, they continue to be available for this purpose or in combination with other analgesic, antihypertensive, antiasthmatic, antispasmodic, or antidiuretic drugs. The combination of barbiturates, such as butalbital with analgesic preparations, is ironic. Not only do barbiturates lack analgesic properties, but at low doses they antagonize the effects of analgesics. Phenobarbital is effective as an anticonvulsant drug (see Chapter 33), and short- and ultrashort-acting barbiturates (Table 34-10) are used for IV anesthesia. Anesthetic doses of barbiturates, such as pentobarbital, are also used to reduce intracranial pressure from cerebral edema associated with head trauma, surgery, or cerebral ischemia.[295] For the induction of this therapeutic coma, sufficient pentobarbital is administered IV to achieve a serum pentobarbital concentration between about 20 and 50 μg/mL. Therefore appropriate analytical methods are necessary to monitor serum pentobarbital concentrations in these circumstances. Moreover, barbiturates continue to be subject to abuse and are a source of intentional or, less commonly, accidental drug intoxication. Measurement of the common barbiturates in serum or urine can aid in the diagnosis and management of barbiturate intoxication.

The general formula for barbiturates is given in Table 34-10. Any change in the constituents at position five that confers an increase in lipid solubility typically results in increased onset of action, decreased duration of action, and increased potency. Moreover an increase in hydrophobic properties also leads to more rapid and extensive hepatic metabolic clearance and thus to decreased urinary elimination of an unchanged drug.

The classification of barbiturates as "ultrashort-acting," "short-acting," "intermediate-acting," and "long-acting" refers to the duration of effect and not to the elimination half-life. The duration of action is determined by the rate of distribution into brain and subsequent redistribution to other tissues.[86]

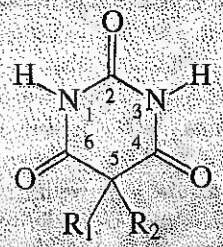
The major manifestations of barbiturate intoxication are CNS, cardiovascular, and respiratory depression. Severe intoxication results in coma, hypothermia, hypotension, and cardiorespiratory arrest.

Appropriate treatment for barbiturate intoxication includes general cardiopulmonary support and measures to prevent further drug absorption and to enhance elimination. Urine alkalinization may enhance the elimination of long-acting barbiturates (e.g., phenobarbital and barbital) but has little effect on intermediate-, short-, or ultrashort-acting barbiturates.

Once filtered by the glomerulus, a nonionized drug may be appreciably reabsorbed by the tubules. The goal of alkalinization is to maintain the urine pH between 7.5 and 8.5. In this pH range, a large fraction of an acidic drug will be ionized, and its elimination in urine will thus be enhanced.

For urine alkalinization to be effective, the drug should have low plasma protein binding, be appreciably eliminated in urine as an unchanged drug, and have a pK_a below 7.4. From an examination of Table 34-10, only phenobarbital (and other long-acting barbiturates [e.g., barbital]) fulfills these criteria. The primary route of elimination of ultrashort-, short-, and intermediate-acting barbiturates is by hepatic metabolism. Thus with the exception of aprobarbital, only small amounts are eliminated in urine as an unchanged drug. Moreover, at pH 8.0, only about 50% of a

TABLE 34-10 Characteristics of Barbiturates



Barbiturate	Duration of Action (hr)	Half-life (hr)	Therapeutic Concentration (μg/mL)	Toxic Concentration (μg/mL)	% Protein Bound	% Excreted Unchanged in Urine	pK_a	R_1	R_2
Ultrashort-Acting									
Thiopental*	0.5	6-7	1-5 (hypnotic) 7-130 (anesthesia)	>10	75-90	0.3	7.6	$-CH_2CH_3$	$-CHCH_2CH_2CH_3$ | CH_3
Short-Acting									
Butalbital	3-4	34-42	–	–	26	3	7.9	$-CH_2CH{=}CH_2$	$-CH_2CHCH_3$ | CH_3
Pentobarbital	3-4	15-30	1-5	>10	65	1	7.9	$-CH_2CH_3$	$-CHCH_2CH_2CH_3$ | CH_3
Secobarbital	3-4	19-34	1-2	>5	46-70	5	7.9	$-CH_2CH{=}CH_2$	$-CHCH_2CH_2CH_3$ | CH_3
Intermediate-Acting									
Amobarbital	6-8	8-42	1-5	>10	59	1-3	7.9	$-CH_2CH_3$	$-CH_2CH_2CHCH_3$ | CH_3
Aprobarbital	6-8	14-34	–	–	55-70	13-24	8.1	$-CH_2CH{=}CH_2$	$-CHCH_3$ | CH_3
Butabarbital	6-8	34-42	–	–	26	5-9	7.9	$-CH_2CH_3$	$-CHCH_2CH_3$ | CH_3
Long-Acting									
Phenobarbital	10-12	40-140	15-40	>65	45-50	25-33	7.2	$-CH_2CH_3$	$-C_6H_5$

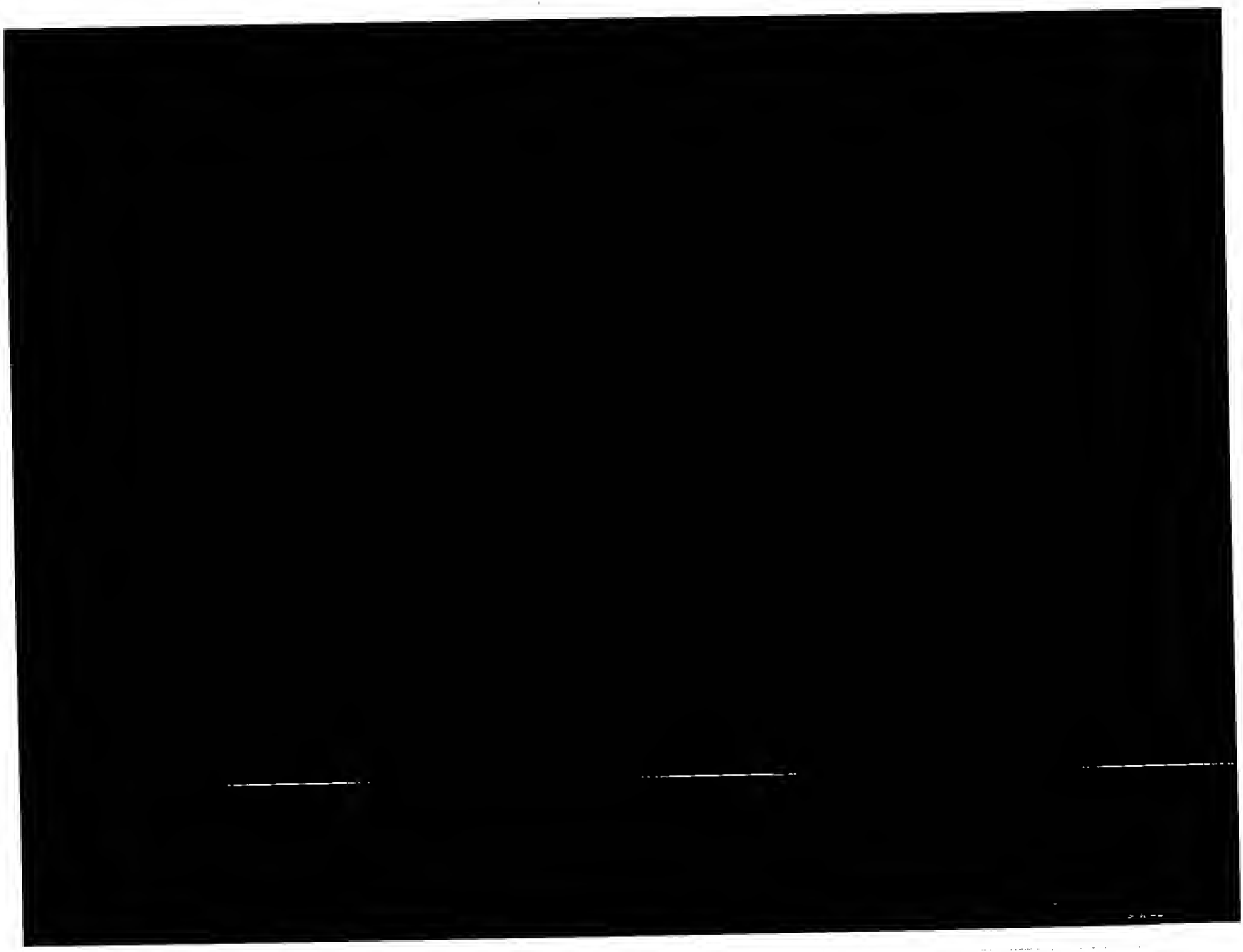
Data from Baselt RC. Disposition of toxic drugs and chemicals in man. 7th ed. Foster City, CA: Biomedical Publications, 2004; Tietz NW, Ed. Clinical guide to laboratory tests. Philadelphia: WB Saunders Co, 1995; and Physician's desk reference. 56th ed. Montvale, NJ: Medical Economics, 2002.
*Oxygen at position 2 is replaced by sulfur.

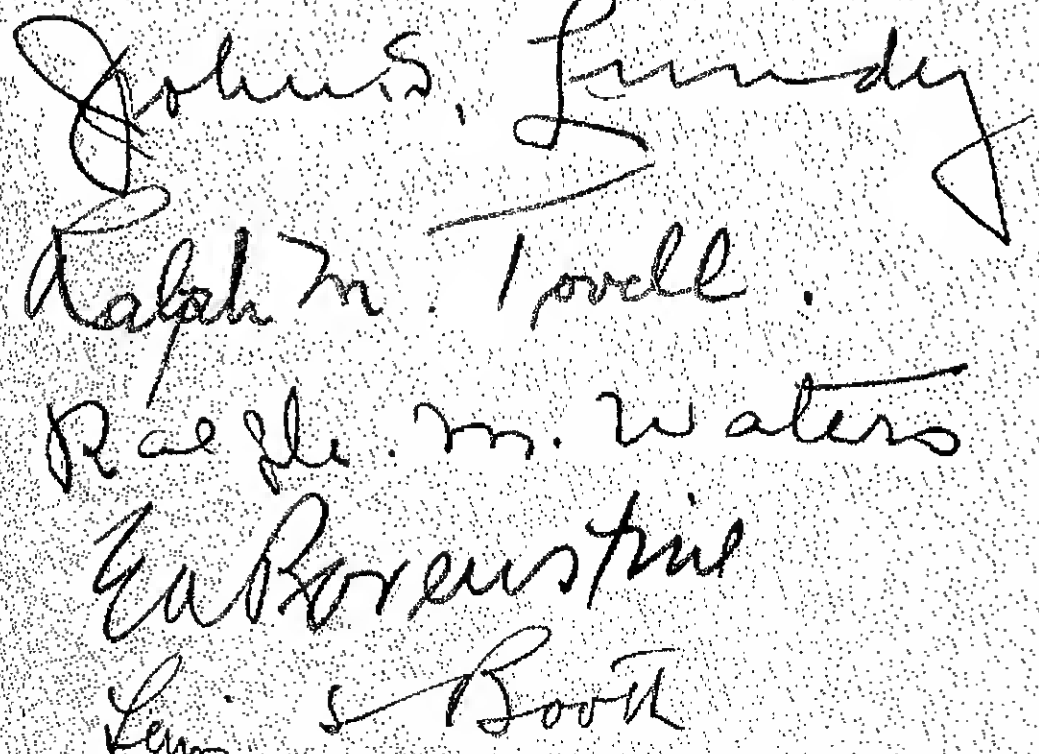
short- or intermediate-acting barbiturate (pK_a 7.9 to 8.1) is ionized, whereas phenobarbital (pK_a 7.2) is about 85% ionized. Hemodialysis is effective in increasing the elimination of all barbiturates. However, it is more effective for long-acting barbiturates than for shorter-acting barbiturates because of differences in their lipid solubility and protein binding. Whereas urine alkalinization may increase the elimination of phenobarbital somewhat, it is considerably less effective than the process referred to as GI dialysis, which is mediated by the repeated oral administration of activated charcoal (multiple-dose activated charcoal, MDAC).[9,131]

The rationale for MDAC therapy is that drug secreted into the GI tract (along with a previously unabsorbed drug) is bound by charcoal and thus cannot be reabsorbed. Drugs that are amenable to this process are ones that have a small volume of distribution, low protein binding, and a prolonged elimination $t_{1/2}$ following overdose. Currently, MDAC is recommended only for the treatment of serious phenobarbital, theophylline, carbamazepine, quinine, and dapsone overdose.[9]

The barbiturates undergo extensive hepatic metabolism in which the C5 substituents are transformed to alcohols, phenols, ketones, or carboxylic acids; these metabolites may be excreted in urine in part as glucuronide conjugates. For some barbiturates (amobarbital and phenobarbital), *N*-glucosylation is an additional important metabolic trans-

EXHIBIT 10





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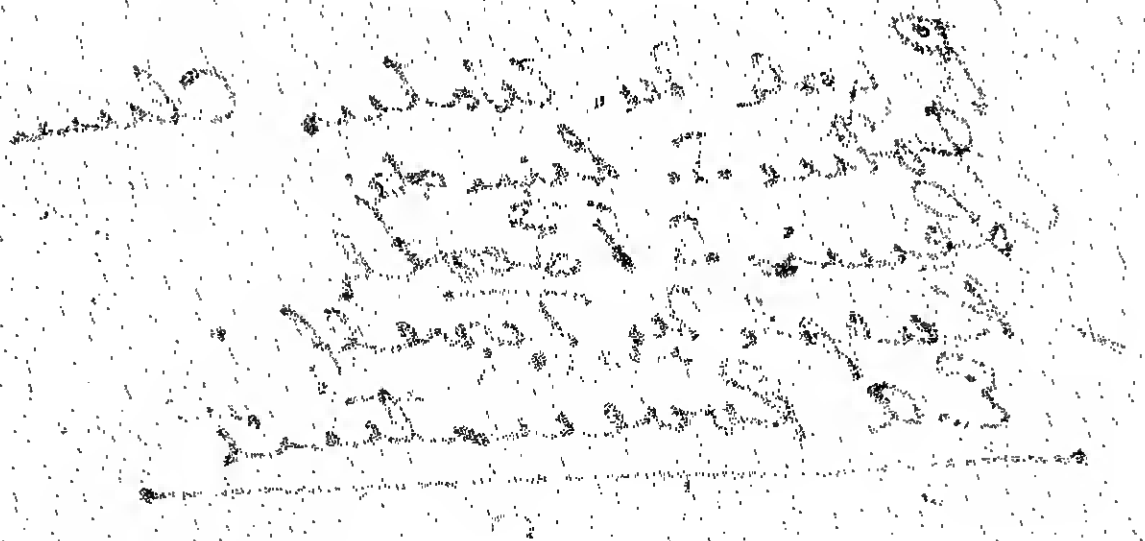

BARBITURIC ACID DERIVATIVES

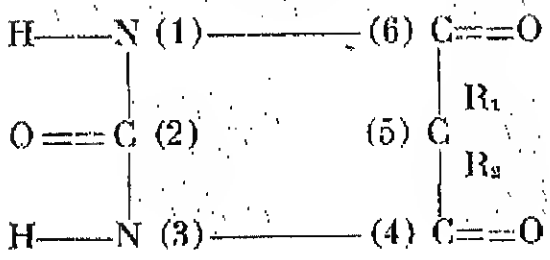

Fig. 20.—The structural formula of barbituric acid. Following is a comparison of certain barbituric acid derivatives, showing how they differ in chemical structure. The barbituric acid derivatives are listed in the order of decreasing duration of action. The numbers which head the columns in the table below refer to the numbers that designate position in the structural formula.

DURATION (Decrease ↓ / Increase ↑)			(5) (R_1)	(5) (R_2)	(1)	(2)
LONG	Phenobarbital (Luminal)	U.S.P.	ethyl	phenyl		
	Barbital (medinal; veronal)	U.S.P.	ethyl	ethyl		
INTERMEDIATE	Dial	N.N.R.	allyl	allyl		
	Ipral	N.N.R.	ethyl	isopropyl		
	Calcium Sodium Alurate	N.N.R.	allyl	isopropyl		
	Neonal	N.N.R.	ethyl	n-butyl		
SHORT	Nostal	N.N.R.	bromallyl	isopropyl		
	Amytal	N.N.R.	ethyl	isoamyl		
	Sandoptal	N.N.R.	allyl	isobutyl		
	Pernoston	N.N.R.	bromallyl	Betahutyl		
	Pentobarbital (Nembutal)	N.N.R.	ethyl	1-methylbutyl		
	Phanodorn	N.N.R.	ethyl	cyclohexenyl		
	Ortal-sodium	N.N.R.	ethyl	n-hexyl		
ULTRA SHORT	Evipal		methyl	cyclohexenyl	methyl	
	Pentothal sodium	N.N.R.	ethyl	1-methylbutyl		thio